

FORM PTO-1390 (REV 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER A0000100-01-SMH
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>10/049762</b>
INTERNATIONAL APPLICATION NO. PCT/US00/18348	INTERNATIONAL FILING DATE 5 July 2000	PRIORITY DATE CLAIMED July 16, 1999	
TITLE OF INVENTION Method for Treating Chronic Pain Using Mek Inhibitors			
APPLICANT(S) FOR DO/EO/US BARRETT, Stephen Douglas, BOOTH, Richard John, BRIDGES, Alexander James, DIXON, Alistair, KAUFMAN, Michael, , LEE, Kevin, PINNOCK, Robert Denham, SCAGGS, Yvonne, TECLE, Haile			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).			
Items 11 to 20 below concern document(s) or information included:			
11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input type="checkbox"/> A FIRST preliminary amendment. 14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A change of power of attorney and/or address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825. 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input checked="" type="checkbox"/> Other items or information: International Search Report (PCT/ISA/210) International Preliminary Examination Report (PCT/IPEA/409) Certificate of Mailing by Express Mail			

Express Mail No. EF378128674US.  
 PD-A0000100-01-SMH

U.S. APPLICATION NO. <b>10/049762</b> <small>(known as 37 CFR 1.53)</small>	INTERNATIONAL APPLICATION NO. <b>PCT/US00/18348</b>	ATTORNEY'S DOCKET NUMBER <b>A0000100-01-SMH</b>
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21. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. .... <b>\$1000.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$860.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... <b>\$710.00</b>  International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$690.00</b>  International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... <b>\$100.00</b>  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>	<b>CALCULATIONS PTO USE ONLY</b>          <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; border-bottom: 1px solid black;">\$ 860.00</td> <td style="width: 40%; border-bottom: 1px solid black;"></td> </tr> <tr> <td style="border-bottom: 1px solid black;">\$ 130.00</td> <td style="border-bottom: 1px solid black;"></td> </tr> </table>	\$ 860.00		\$ 130.00	
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Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; border-bottom: 1px solid black;">\$</td> <td style="width: 40%; border-bottom: 1px solid black;"></td> </tr> <tr> <td style="border-bottom: 1px solid black;">\$</td> <td style="border-bottom: 1px solid black;">130.00</td> </tr> </table>	\$		\$	130.00
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CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	125 - 20 =	105	x \$18.00	\$	1,890.00
Independent claims	4 - 3 =	1	x \$80.00	\$	80.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00	\$	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$	2,960.00

<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.	\$ +	
<b>SUBTOTAL =</b>		\$
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	\$	
<b>TOTAL NATIONAL FEE =</b>		\$ 2,960.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +	\$	
<b>TOTAL FEES ENCLOSED =</b>		\$ 2,960.00
		Amount to be refunded: \$ charged: \$

a. ☐ A check in the amount of \$ \_\_\_\_\_ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 23-0455 in the amount of \$ 2,960.00 to cover the above fees.  
 A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any  
 overpayment to Deposit Account No. 23-0455. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card  
 information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR  
 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO Suzanne M. Harvey Warner-Lambert Company Patent Department 2800 Plymouth Road Ann Arbor, Michigan 48105 Telephone: (734) 622-2658 Facsimile: (734) 622-1553	 SIGNATURE <hr style="width: 80%; margin: 0 auto;"/> Suzanne M. Harvey NAME <hr style="width: 80%; margin: 0 auto;"/> 42,640 REGISTRATION NUMBER
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A0000100-01-SMH

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT : Stephen Douglas Barrett, et al. EXAMINER :  
SERIAL NO. : 10/049762 ART UNIT :  
FILED : January 16, 2002 PAPER NO :  
FOR : METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

**Preliminary Amendment**

Commissioner for Patents  
Box PCT  
Washington, D.C. 20231

Dear Sir:

Please amend the above-identified application as follows:

**IN THE SPECIFICATION**

**CLEAN COPY – PLEASE ENTER**

Please add the following new paragraph on page 1, after the title and before line 5:

This application is a 371 application of PCT/US00/18348 filed July 5, 2000, which claims the benefit of priority to United States provisional application Serial No. 60/144,659 filed July 16, 1999, United States provisional application Serial No. 60/144,658 filed July 16, 1999, United States provisional application Serial No. 60/144,655 filed July 16, 1999, United States provisional application Serial No. 60/144,419 filed July 16, 1999, United States provisional application Serial No. 60/144,320 filed July 16, 1999, and United States provisional application Serial No. 60/144,280 filed July 16, 1999,

REMARKSI. Priority

In accordance with 35 U.S.C. §119(e) and 35 U.S.C. §120, the Applicants have submitted an amendment containing a specific reference to the prior filed applications in the section above entitled "In the Specification". The Applicants note that a petition and surcharge are not required to correct this priority claim, because the Applicants have amended the first sentence of the specification to contain the specific reference within the later of 4 months from the date on which the National Stage commenced under 35 U.S.C. 371 or 16 months from the filing of the prior filed application.

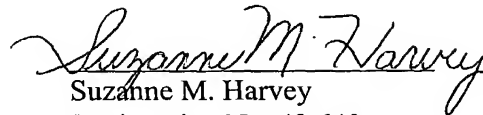
Conclusion

The Applicants respectfully request entry of the present amendment.

If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at 734-622-2658.

Respectfully submitted,

Dated: May 16, 2002



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## **METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS**

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### **BACKGROUND**

The invention features a method for treating chronic pain using MEK inhibitors. Chronic pain includes neuropathic pain, and chronic inflammatory pain.

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Abnormality anywhere in a nerve pathway disrupts nerve signals, which in turn are abnormally interpreted in the brain, causing neuropathic pain. Neuropathic pain may be, for example, a deep ache, a burning sensation, or hypersensitivity to touch. Diseases or conditions associated with neuropathic pain include, without limitation, diabetic neuropathy, causalgia, plexus avulsion, neuroma, vasculitis, crush injury, viral infections (e.g., herpes virus infection or HIV), constriction injury, tissue injury, nerve injury from the periphery to the central nervous system, limb amputation, hypothyroidism, uremia, chronic alcoholism, post-operative pain, arthritis, back pain, and vitamin deficiencies.

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Infections such as herpes zoster (shingles) can cause nerve inflammation and produce postherpetic neuralgia, a chronic burning localized to the area of viral infection. Hyperalgesia is when an already noxious stimulus becomes more painful, and allodynia, when a previously non-noxious stimulus becomes painful (such as contact of clothing or a breeze). Reflex sympathetic dystrophy is accompanied by swelling and sweating or changes in local blood flow, tissue atrophy, or osteoporosis. Causalgia, including severe burning pain and swelling, sweating, and changes in blood flow, may follow an injury or disease of a major nerve such as the sciatic nerve. Some types of chronic low back pain can have a neuropathic component (e.g., sciatica, postpoliomyelitis and CPRM).

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Neuropathic pain may also be induced by cancer or chemotherapy.

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Neuropathic pain is currently treated with anticonvulsants such as carbamazepine and antidepressants such as amitryptiline. NSAIDS and opioids

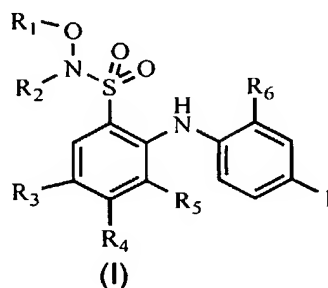
generally have little effect (*Fields et al 1994 Textbook of Pain p 991-996 (pub: Churchill Livingstone), James & Page 1994 J.Am.Pediatr.Med.Assoc, 8: 439-447, Galer, 1995 Neurology 45 S17-S25*. Neuropathic conditions that have been treated with gabapentin include: postherpetic neuralgia, postpoliomyelitis, CPRM, HIV-related neuropathy, trigeminal neuralgia, and reflex sympathetic dystrophy (RSD). The generally weak efficacy of antiinflammatory agents suggests that the mechanism for chronic pain is separate from hyperalgesia.

### SUMMARY OF THE INVENTION

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The invention features a method for treating chronic pain, which method includes the step of administering a composition including a MEK inhibitor to a patient in need of such treatment. Chronic pain includes neuropathic pain, idiopathic pain, and pain associated with vitamin deficiencies, uremia, hypothyroidism post-operative pain, arthritis, back pain, and chronic alcoholism. The invention also features compositions as disclosed, formulated for the treatment of chronic pain. Such a composition may include one or more MEK inhibitor compounds having a structure disclosed in patent applications USSN 60/115,652, filed January 13, 1999, USSN 60/115,670, filed January 13, 1999, USSN 60/115,876 filed January 13, 1999, USSN 60/115,874, PCT/US99/30417, international filing date December 21, 1999, PCT/US99/30418, international filing date December 21, 1999, PCT/US99/30491, international filing date December 21, 1999, and PCT/US99/30435, international filing date December 21, 1999.

Examples of MEK inhibitors include a compound having the formula (I) below:



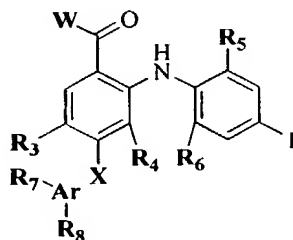
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$R_1$  is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub> cycloalkyl)-C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl, (CH<sub>2</sub>)<sub>2-4</sub> OR<sub>C</sub> or (CH<sub>2</sub>)<sub>2-4</sub> NR<sub>C</sub>R<sub>D</sub>.  $R_2$  is H, C<sub>1-4</sub> alkyl, phenyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical, or (C<sub>3-6</sub> cycloalkyl) methyl. Each of  $R_3$  and  $R_4$  is independently selected from H, F, NO<sub>2</sub>, Br and Cl.  $R_5$  is selected from H and F.  $R_6$  is H, F, Cl or CH<sub>3</sub>. Each of  $R_C$  and  $R_D$  is independently selected from H, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, and phenyl; or NR<sub>C</sub>R<sub>D</sub> may be a piperidino, morpholino, or N-(C<sub>1-6</sub> alkyl)piperazino ring. Each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>. Each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxyl, amino, and NO<sub>2</sub>. The invention also includes a pharmaceutically acceptable salt or C<sub>1-8</sub> ester of a disclosed compound. For example, the disclosed alcohol compounds may form esters having the structure obtained by replacing the H of a hydroxyl group with a -C(=O)C<sub>1-7</sub> acyl group.

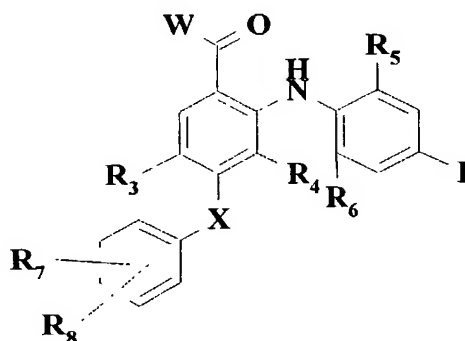
The invention also relates to a pharmaceutical composition including

(a) a compound of formula (I) and (b) a pharmaceutically-acceptable carrier.

The invention also features the use of compounds of formulae (II)A below, such as formula (I)A:



(II)A



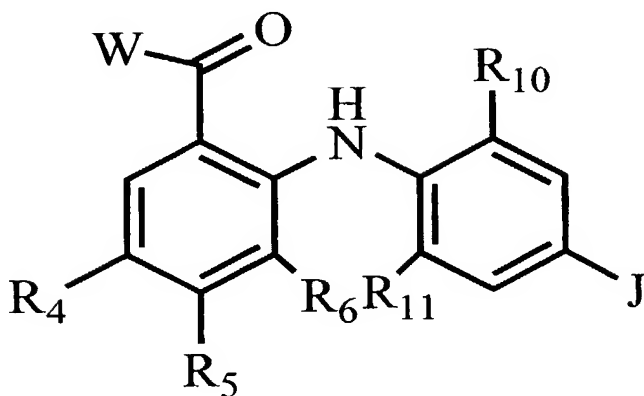
(I)A

In formulae (I)A and (II)A, W is OR<sub>1</sub>, NR<sub>2</sub>OR<sub>1</sub>, NR<sub>A</sub>R<sub>B</sub>, NR<sub>2</sub>NR<sub>A</sub>R<sub>B</sub>, or NR<sub>2</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>A</sub>R<sub>B</sub>. R<sub>1</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub> cycloalkyl)-C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl, or (CH<sub>2</sub>)<sub>2-4</sub>NR<sub>A</sub>R<sub>B</sub>. R<sub>2</sub> is H, phenyl, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or (C<sub>3-8</sub>

cycloalkyl)C<sub>1-4</sub> alkyl. R<sub>A</sub> is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (aminosulfonyl)phenyl, [(aminosulfonyl)phenyl]C<sub>1-4</sub> alkyl, (aminosulfonyl)C<sub>1-6</sub> alkyl, (aminosulfonyl)C<sub>3-6</sub> cycloalkyl, or [(aminosulfonyl)C<sub>3-6</sub> cycloalkyl]C<sub>1-4</sub> alkyl. R<sub>B</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or C<sub>6-8</sub> aryl. R<sub>3</sub> is halo, NO<sub>2</sub>, SO<sub>2</sub>NR<sub>I</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>E</sub>R<sub>F</sub>, SO<sub>2</sub>NR<sub>I</sub>R<sub>K</sub> or (CO)T. T is C<sub>1-8</sub> alkyl, C<sub>3-8</sub> cycloalkyl, (NR<sub>E</sub>R<sub>F</sub>)C<sub>1-4</sub> alkyl, OR<sub>F</sub>, NR<sub>I</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>E</sub>R<sub>F</sub>, or NR<sub>E</sub>R<sub>F</sub>. R<sub>4</sub> is H or F; R<sub>5</sub> is H, methyl, halo, or NO<sub>2</sub>; and R<sub>6</sub> is H, methyl, halo, or NO<sub>2</sub>. In formula (II)A, Ar is phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl. Each of R<sub>7</sub> and R<sub>8</sub> is independently selected from H, halo, C<sub>1-4</sub> alkyl, SO<sub>2</sub>NR<sub>J</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, (CO)(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, (CO)NR<sub>J</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, (CO)O(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, SO<sub>2</sub>NR<sub>G</sub>R<sub>H</sub>, and (CO)NR<sub>G</sub>R<sub>H</sub>. However, where Ar is a pyridyl, each of R<sub>7</sub> and R<sub>8</sub> is H. Each of R<sub>C</sub>, R<sub>D</sub>, R<sub>E</sub>, R<sub>F</sub>, R<sub>G</sub>, and R<sub>H</sub> is independently selected from H, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, and phenyl. Each of NR<sub>C</sub>R<sub>D</sub>, NR<sub>E</sub>R<sub>F</sub>, and NR<sub>G</sub>R<sub>H</sub> can also be independently morpholinyl, piperazinyl, pyrrolidinyl, or piperadiny. Each of R<sub>I</sub> and R<sub>J</sub> is independently H, methyl, or ethyl. R<sub>K</sub> is C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, or phenyl. X is O, S, or NH. Finally, each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-4</sub> alkenyl, C<sub>1-4</sub> alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxyl, amino, and NO<sub>2</sub>. In addition to the above compounds, the invention also provides a pharmaceutically acceptable salt or C<sub>1-7</sub> ester thereof.

The invention also relates to a pharmaceutical composition including (a) a diarylamine, e.g., of formula (I)A, and (b) a pharmaceutically acceptable carrier.

The invention also features the use of a compound having the formula (I)B below:



(I)B

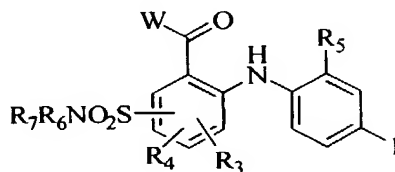
- In formula (I)B, W is OR<sub>1</sub>, NR<sub>2</sub>OR<sub>1</sub>, NR<sub>A</sub>R<sub>B</sub>, NR<sub>2</sub>NR<sub>A</sub>R<sub>B</sub>, O(CH<sub>2</sub>)<sub>1-4</sub>NR<sub>A</sub>R<sub>B</sub>, or NR<sub>2</sub>(CH<sub>2</sub>)<sub>1-4</sub>NR<sub>A</sub>R<sub>B</sub>. R<sub>1</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)-C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, or (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl. Each of R<sub>2</sub> and R<sub>3</sub> is independently H, phenyl, C<sub>1-4</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl. Each of R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> is independently H, F, Br, Cl, or NO<sub>2</sub>. R<sub>A</sub> is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (aminosulfonyl)phenyl, (aminosulfonyl)-phenyl] C<sub>1-4</sub> alkyl, (aminosulfonyl)C<sub>1-6</sub> alkyl, (aminosulfonyl)C<sub>3-6</sub> cycloalkyl, or [(aminosulfonyl)C<sub>3-6</sub> cycloalkyl]C<sub>1-4</sub> alkyl. R<sub>B</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or phenyl. J is SR<sub>C</sub>, OR<sub>C</sub>, SO<sub>2</sub>R<sub>C</sub>, SOR<sub>C</sub>, SO<sub>2</sub>NR<sub>D</sub>R<sub>E</sub>, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>5-8</sub> cycloalkenyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)-C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical (e.g., 1,2,5-thiadiazol-3-yl),

- (C<sub>3-8</sub> heterocyclic radical) C<sub>1-4</sub> alkyl, -M'-E'-G', (heterocyclic radical)-M'-E'-G', or (cycloalkyl)-M'-E'-G'. M' is O, SO, SO<sub>2</sub>, NR<sub>E</sub>, (CO)NR<sub>E</sub>, NR<sub>E</sub>(CO), SO<sub>2</sub>NR<sub>E</sub>, NR<sub>E</sub>SO<sub>2</sub>, or CH<sub>2</sub>. E' is absent (in other words, a covalent bond), (CH<sub>2</sub>)<sub>1-4</sub> or (CH<sub>2</sub>)<sub>m</sub>O(CH<sub>2</sub>)<sub>p</sub> where 1 ≤ (each of m and p independently) ≤ 3 and 2 ≤ (m + p) ≤ 3
4. G' is OR<sub>3</sub>, SOR<sub>C</sub>, SO<sub>2</sub>R<sub>C</sub>, or NR<sub>F</sub>R<sub>G</sub>; provided that where p = 1, then G' is H. Each of R<sub>C</sub>, R<sub>D</sub>, R<sub>E</sub>, R<sub>F</sub> and R<sub>G</sub> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical, and phenyl; NR<sub>F</sub>R<sub>G</sub> and NR<sub>D</sub>R<sub>E</sub> can each also independently be selected from morpholinyl, piperazinyl, pyrrolidinyl, or piperidinyl. R<sub>10</sub> is H, C<sub>1-4</sub> alkyl, halo, NO<sub>2</sub>, or SO<sub>2</sub>NR<sub>H</sub>R<sub>I</sub>. R<sub>11</sub> is H, halo, or NO<sub>2</sub>.

- Each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, phenyl, hydroxy, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxy, amino, and NO<sub>2</sub>. The invention also encompasses a pharmaceutically acceptable salt or C<sub>1-7</sub> ester of a compound of formula (I)B.

- The invention also relates to a pharmaceutical composition including (a) a compound of formula (I)B and (b) a pharmaceutically-acceptable carrier.

The invention also features the use of a compound having the formula (I)C below:



(I)C

W is  $OR_1$ ,  $NR_2OR_1$ ,  $NR_AR_B$ ,  $NR_2NR_AR_B$ , or  $NR_2(CH_2)_{2-4}NR_AR_B$ .  $R_1$  is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub> cycloalkyl)-C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl, or  $(CH_2)_{2-4}NR_AR_B$ .  $R_2$  is H, phenyl, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl.  $R_A$  is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (aminosulfonyl)phenyl, [(aminosulfonyl)phenyl]C<sub>1-4</sub> alkyl, (aminosulfonyl)C<sub>1-6</sub> alkyl, (aminosulfonyl)C<sub>3-6</sub> cycloalkyl, or [(aminosulfonyl)C<sub>3-6</sub> cycloalkyl]C<sub>1-4</sub> alkyl.  $R_B$  is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or C<sub>6-8</sub> aryl.  $R_3$  is H, F, Cl, Br, or NO<sub>2</sub>.  $R_4$  is H or F.  $R_5$  is H, methyl or Cl.  $R_6$  is H, C<sub>1-4</sub> alkyl, hydroxyethyl, hydroxypropyl,  $(CH_2)_{2-4}(NR_CR_D)$ , phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl or CH<sub>2</sub>Ar, where Ar is phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl.  $R_7$  is H, C<sub>1-4</sub> alkyl, hydroxyethyl, hydroxypropyl,  $(CH_2)_{2-4}(NR_CR_D)$ , phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, or CH<sub>2</sub>Ar, where Ar is phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl. Each of  $R_C$  and  $R_D$  is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical, and phenyl.  $NR_CR_D$  can also be selected from morpholinyl, piperazinyl, pyrrolidinyl, or piperadinyl. Each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, phenyl, hydroxy, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxy, amino, and NO<sub>2</sub>. The invention also features pharmaceutically acceptable salts and C<sub>1-7</sub> esters thereof.

Preferred compounds include PD 297764, 3,4-Difluoro-2-(4-iodo-phenylamino)-N-methoxy-5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-benzamide;



PD 297765, N-Allyloxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(4-methyl-piperazine-1-sulfonyl)-benzamide; PD297766, N-Allyloxy-5-[(2-diethylamino-ethyl)-methyl-sulfamoyl]-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; PD297767, N-Allyloxy-5-[(3-dimethylamino-propyl)-methyl-sulfamoyl]-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; PD297768, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(4-methyl-piperazine-1-sulfonyl)-benzamide; PD297769, N-Cyclopropylmethoxy-5-[(2-diethylamino-ethyl)-methyl-sulfamoyl]-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; PD297770, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-[methyl-(2-pyridin-2-yl-ethyl)-sulfamoyl]-benzamide; PD297771, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-benzamide; PD297772, 5-[Benzyl-(2-dimethylamino-ethyl)-sulfamoyl]-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; PD297773, 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-benzamide; and PD297774, 1-[5-Allyloxycarbamoyl-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonyl]-piperidine-3-carboxylic acid amide.

Preferred embodiments of the invention include methods using one or more of the following compounds:

- (a) said MEK inhibitor has a structure selected from: 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; and 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide;
- (b) said MEK inhibitor has a structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid;
- (c) said MEK inhibitor has a structure selected from: 2-(4-ethynyl-2-methyl-phenylamino)-4-fluoro-benzoic acid; and 2-(3',5'-dichloro-biphenyl-4-ylamino)-benzoic acid; and
- (d) said MEK inhibitor has a structure selected from: 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-5-sulfamoyl-benzamide; C-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-dimethylsulfamoyl-difluoro-benzamide; N-cyclopropylmethoxy-dimethylsulfamoyl-difluoro-C-(4-iodo-2-

methyl-phenylamino)-benzamide; and C-(2-chloro-4-iodo-phenylamino)-difluoro-(methoxy-methyl-sulfamoyl)-N-(2-morpholin-4-yl-ethoxy)benzamide.

The invention also relates to a pharmaceutical composition including  
5 (a) a compound of formula (I)C and (b) a pharmaceutically-acceptable carrier.

### BRIEF DESCRIPTION OF THE FIGURES

10 FIG. 1 is a bar graph representing the paw withdrawal threshold (PWT) in grams as a function of time in days. The empty, cross-hatched, and single-hatched bars are vehicle, PD 198306, and pregabalin, respectively. The arrows indicate time of drug administration (30 mg/kg, p.o.).

15 FIG 2. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were  
20 repeated twice a day for two days. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

25 FIG. 3. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were  
30 repeated twice a day for two days. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup>

quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

FIG. 4. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30µg/10µl), or pregabalin (100µg/10µl) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median ± 1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-9).

FIG. 5. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30µg/10µl), or pregabalin (100µg/10µl) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median ± 1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-8).

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FIG. 6 is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Animals received a single intraplantar (i.pl.) administration of PD 198306 (3mg/100µl), or an intrathecal injection of PD 198306 (30µg/10µl) and withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median ± 1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-9).

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FIG. 7. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Animals received a single intraplantar (i.pl.) administration of PD 198306 (3mg/100µl), or

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an intrathecal injection of PD 198306 (30 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

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FIG. 8 is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD219622, PD297447, PD 184352, or PD 254552 (30 $\mu$ g/10 $\mu$ l), or pregabalin (100 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

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#### DETAILED DESCRIPTION

The compounds disclosed herein are pharmaceutically active, for example, they inhibit MEK. MEK enzymes are dual specificity kinases involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis.

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Defects include a change either in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade. The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound

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state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

- 5           Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK<sub>1</sub> and MEK<sub>2</sub>) which then activates MAP kinase, ERK (ERK<sub>1</sub> and ERK<sub>2</sub>). Activation of MAP kinase by mitogens appears to be essential for
- 10 proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of Raf and other
- 15 kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S218 and S222 in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y185, and a threonine residue, T183, separated by a single amino acid.
- 20           This double phosphorylation activates MAP kinase at least 100-fold. Activated MAP kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to
- 25 Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than the MAP kinase, ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or
- 30 even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that

phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating  
5 through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

The effect of the MEK inhibitor PD 198306 has been investigated in two animal models of neuropathic pain by assessing static allodynia with von Frey hairs.

Oral administration of PD 198306 (3-30mg/kg) had no effect in the model of  
10 chronic constriction injury of the sciatic nerve (CCI). However, after repeated administration (3 doses over two days) it had a transient effect in the diabetic neuropathy model (streptozocin). This may be due to disorders of the blood-brain barrier induced by the diabetic condition in these animals, thus allowing central action of the compound. Intrathecal administration of PD 198306 (1-30 $\mu$ g) dose-  
15 dependently blocked static allodynia in both the streptozocin and the CCI models of neuropathic pain, with minimum effective doses (MED) of 3 and 10 $\mu$ g respectively. The highest dose used (30 $\mu$ g) totally blocked the maintenance of static allodynia, for up to 1h. Intraplantar administration of PD 198306 (3mg/100 $\mu$ l) at a dose 100-  
fold higher than the dose shown to be effective intrathecally (30 $\mu$ g/10 $\mu$ l) had no  
20 effect on static allodynia in either of the neuropathic pain models. This finding confirms the lack of effect seen after systemic administration and suggests a central site of action for the compound.

From this study we can suggest the use of MEK inhibitors as potential new therapeutic tools for chronic pain. The study of potential side-effects, especially  
25 related to memory, of future brain-penetrant MEK inhibitors will indicate the therapeutic window for this novel class of compounds in the treatment of pain.

## A. Terms

Certain terms are defined below and by their usage throughout this disclosure.

Alkyl groups include aliphatic (i.e., hydrocarbyl or hydrocarbon radical structures containing hydrogen and carbon atoms) with a free valence. Alkyl groups are understood to include straight chain and branched structures. Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, and octyl. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Alkyl groups can be substituted with 1, 2, 3 or more substituents which are independently selected from halo (fluoro, chloro, bromo, or iodo), hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-dimethylaminobutyl, methoxymethyl, N-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

Alkenyl groups are analogous to alkyl groups, but have at least one double bond (two adjacent  $sp^2$  carbon atoms). Depending on the placement of a double bond and substituents, if any, the geometry of the double bond may be *entgegen* (E), or *zusammen* (Z), *cis*, or *trans*. Similarly, alkynyl groups have at least one triple bond (two adjacent  $sp$  carbon atoms). Unsaturated alkenyl or alkynyl groups may have one or more double or triple bonds, respectively, or a mixture thereof; like alkyl groups, unsaturated groups may be straight chain or branched, and they may be substituted as described both above for alkyl groups and throughout the disclosure by example. Examples of alkenyls, alkynyls, and substituted forms include *cis*-2-butenyl, *trans*-2-butenyl, 3-butylnyl, 3-phenyl-2-propynyl, 3-(2'-fluorophenyl)-2-propynyl, 3-methyl(5-phenyl)-4-pentylnyl, 2-hydroxy-2-propynyl, 2-methyl-2-propynyl, 2-propenyl, 4-hydroxy-3-butylnyl, 3-(3-fluorophenyl)-2-propynyl, and 2-methyl-2-propenyl. In formula (I), alkenyls and alkynyls can be  $C_{2-4}$  or  $C_{2-8}$ , for example, and are preferably  $C_{3-4}$  or  $C_{3-8}$ .

More general forms of substituted hydrocarbon radicals include hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, and corresponding forms for the prefixes amino-, halo- (e.g., fluoro-, chloro-, or bromo-), nitro-, alkyl-, phenyl-, cycloalkyl- and so on, or combinations of substituents. According to formula (I), therefore, substituted alkyls include hydroxyalkyl, aminoalkyl, nitroalkyl, haloalkyl, alkylalkyl (branched alkyls, such as methylpentyl), (cycloalkyl)alkyl, phenylalkyl, alkoxy, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, aryloxyalkyl, arylalkyloxyalkyl, (heterocyclic radical)alkyl, and (heterocyclic radical)oxyalkyl.  $R_1$  thus includes hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminocycloalkyl, aminoaryl, alkylalkenyl, (alkylaryl)alkyl, (haloaryl)alkyl, (hydroxyaryl)alkynyl, and so forth. Similarly,  $R_A$  includes hydroxyalkyl and aminoaryl, and  $R_B$  includes hydroxyalkyl, aminoalkyl, and hydroxyalkyl(heterocyclic radical)alkyl.

Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, and their nonaromatic counterparts. Further examples of heterocyclic radicals include piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, octahydrobenzothiofuranyl, and octahydrobenzofuranyl.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an  $IC_{50}$  for MEK 1 or MEK 2 that is at least one-fiftieth ( $1/50$ ) that of its  $IC_{50}$  for one of the above-named other enzymes. Preferably, a selective inhibitor has an  $IC_{50}$  that is at least  $1/100$ , more preferably  $1/500$ , and even more preferably  $1/1000$ ,  $1/5000$ , or less than that of its  $IC_{50}$  or one or more of the above-named enzymes.



## B. Compounds

One aspect of the invention features the use of disclosed compounds shown in formula (I) in the Summary section.

- 5           Embodiments of the invention include compounds wherein: (a)  $R_3$  is bromo or chloro; (b)  $R_4$  is fluoro; (c)  $R_5$  is H; (d) each of  $R_4$  and  $R_5$  is H; (e) each of  $R_4$  and  $R_5$  is fluoro; (f)  $R_3$  is bromo; (g)  $R_3$  is fluoro; (h)  $R_4$  is nitro; (i)  $R_5$  is H; (j)  $R_6$  is chloro; (k)  $R_6$  is methyl; (l)  $R_1$  is H or  $C_{1-4}$  alkyl, and  $R_2$  is H; (m)  $R_1$  is ( $C_{3-6}$  cycloalkyl)methyl; (n)  $R_1$  is H; (o)  $R_1$  is  $(CH_2)_{2-4}OR_C$  or  $(CH_2)_{2-4}NR_CR_D$ ;  
10       (p)  $R_6$  is chloro or methyl; (q)  $R_6$  is H; or combinations thereof.

Preferably, when  $R_1$ ,  $R_C$ , or  $R_D$  is an alkenyl or alkynyl, the double or triple bond, respectively, is not adjacent the point of attachment when the point of attachment is a heteroatom. For example,  $R_1$  is preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

- 15           Examples of compounds of formula (I) include: 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 4-fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4,5-trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 5-bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonic acid; N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide; or  
20           N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide.  
25             
30

Further examples of compounds include: 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-4-nitro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzenesulfonamide; or 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzenesulfonamide.

A second aspect of the invention features the use of compounds shown in formulae (I)A and (II)A in the Summary section. Embodiments of the invention includes compounds of formula (I)A wherein: (a)  $R_3$  is  $\text{NO}_2$ ; (b)  $R_4$  is fluoro; (c) each of  $R_3$  and  $R_4$  is independently selected from H and fluoro; (d)  $R_5$  is methyl, fluoro, or chloro; (e)  $R_6$  is methyl, chloro, fluoro, nitro, or hydrogen; (f)  $R_6$  is H; (g)  $R_6$  is fluoro; (h)  $R_K$  is methyl or ethyl; (i)  $R_1$  is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenyl, phenethyl, allyl,  $\text{C}_{3-5}$  alkenyl,  $\text{C}_{3-6}$  cycloalkyl, ( $\text{C}_{3-5}$  cycloalkyl) $\text{C}_{1-2}$  alkyl, ( $\text{C}_{3-5}$  heterocyclic radical) $\text{C}_{1-2}$  alkyl, or  $(\text{CH}_2)_{2-4}\text{NR}_\text{C}\text{R}_\text{D}$ ; (j)  $R_1$  is H or ( $\text{C}_{3-4}$  cycloalkyl) $\text{C}_{1-2}$  alkyl; (k)  $R_2$  is H or methyl; (l)  $R_A$  has at least one hydroxyl substituent; (m)  $R_A$  is H, methyl, ethyl, isobutyl, hydroxyethyl, phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxy-propyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and  $R_B$  is H; or where  $R_B$  is methyl and  $R_A$  is phenyl; (n) W is  $\text{NR}_\text{A}\text{R}_\text{B}$  or  $\text{NR}_2\text{NR}_\text{A}\text{R}_\text{B}$ ; (o) W is  $\text{NR}_2(\text{CH}_2)_{2-4}\text{NR}_\text{A}\text{R}_\text{B}$  or  $\text{O}(\text{CH}_2)_{2-3}\text{NR}_\text{A}\text{R}_\text{B}$ ; (p) W is  $\text{NR}_2\text{OR}_1$ ;

(q) W is OR<sub>B</sub>; (r) R<sub>7</sub> is in the para position relative to X; (s) R<sub>7</sub> is iodo; (t) R<sub>8</sub> is in the ortho position relative to X; (u) or combinations thereof.

In additional embodiments, if R<sub>6</sub> is H, then R<sub>5</sub> is nitro; or R<sub>6</sub> is methyl, halo, or nitro; or R<sub>3</sub> is SO<sub>2</sub>NR<sub>I</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>E</sub>R<sub>F</sub>, SO<sub>2</sub>NR<sub>I</sub>R<sub>K</sub> or (CO)T. In some  
 5 embodiments, Ar is phenyl (e.g., formula (I)A), and in other embodiments, Ar is 2-pyridyl, 3-pyridyl, or 4-pyridyl. Preferably, where one of R<sub>1</sub>, R<sub>2</sub>, R<sub>A</sub>, R<sub>B</sub>, R<sub>C</sub>, and R<sub>D</sub> is an alkenyl or alkynyl group, the double or triple bond, respectively, is not adjacent the point of attachment. For example, where W is NR<sub>2</sub>OR<sub>1</sub>, R<sub>2</sub> is preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-  
 10 1-enyl. Some embodiments include the formula 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid, the compounds in the following list, and 2-methyl (instead of 2-chloro) analogs thereof.

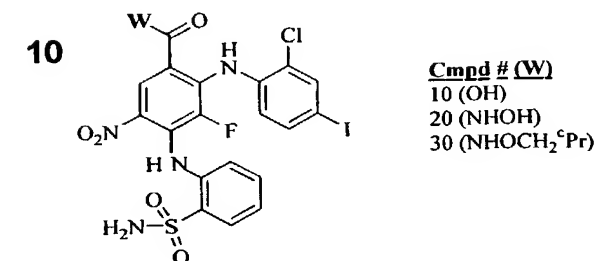
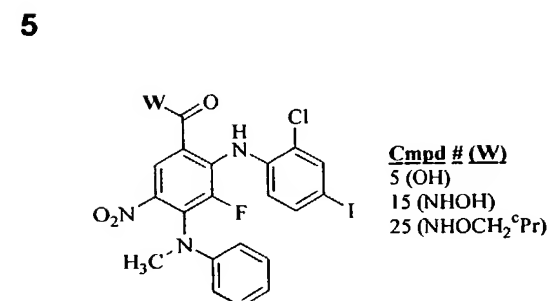
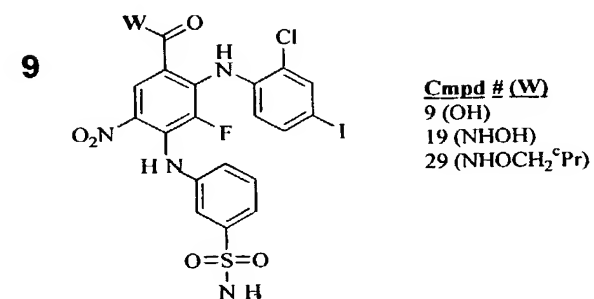
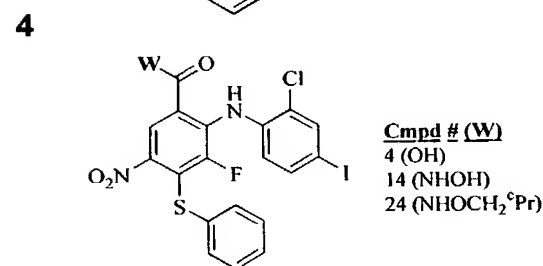
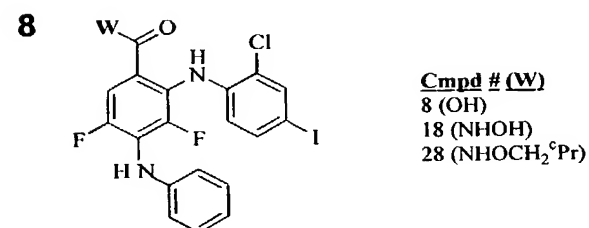
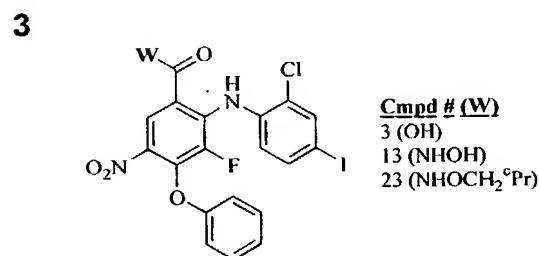
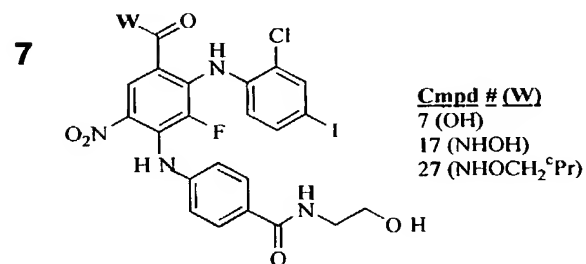
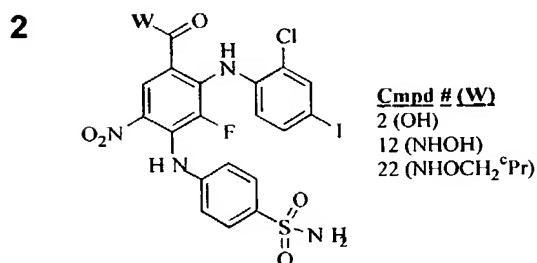
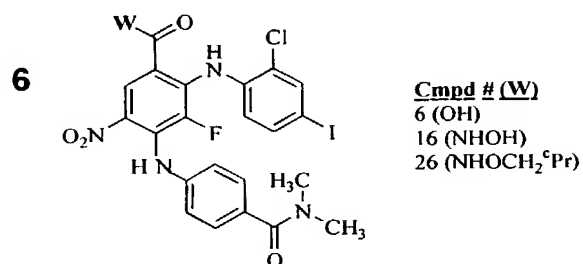
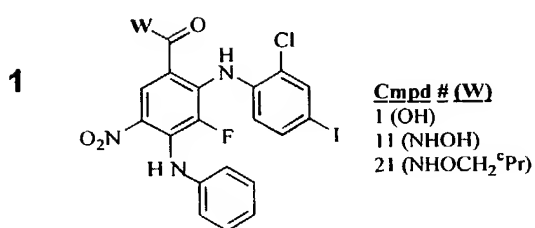
1. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-(4-sulfamoyl-  
 15 phenylamino)-benzoic acid;
2. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-phenylamino-benzoic acid;
3. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-phenoxy-benzoic acid;
4. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-phenylsulfanyl-benzoic  
 20 acid;
5. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-4-(methyl-phenyl-amino)-5-nitro-benzoic acid;
6. 2-[(2-chloro-4-iodophenyl)amino]-3-fluoro-4-[[4-[(2-hydroxyethyl)amino]-  
 carbonyl]phenyl]amino]-5-nitro-benzoic acid;
- 25 7. 2-[(2-chloro-4-iodophenyl)amino]-4-[[4-[(dimethylamino)carbonyl]  
 phenyl]amino]-3-fluoro-5-nitro-benzoic acid;
8. 2-(2-Chloro-4-iodo-phenylamino)-3,5-difluoro-4-phenylamino-benzoic acid;
9. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-(3-sulfamoyl-  
 phenylamino)-benzoic acid;
- 30 10. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-(2-sulfamoyl-  
 phenylamino)-benzoic acid;

11. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-N-hydroxy-5-nitro-4-(4-sulfamoyl-phenylamino)-benzamide;
12. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-N-hydroxy-5-nitro-4-phenylamino-benzamide;
- 5 13. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-N-hydroxy-5-nitro-4-phenoxy-benzamide;
14. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-N-hydroxy-5-nitro-4-phenylsulfanyl-benzamide;
15. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-N-hydroxy-4-(methyl-phenyl-amino)-5-nitro-benzamide;
- 10 16. 2-[(2-chloro-4-iodophenyl)amino]-3-fluoro-N-hydroxy-4-[[4-[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-5-nitro-benzamide;
17. 2-[(2-chloro-4-iodophenyl)amino]-4-[[4-[(dimethylamino)carbonyl]phenyl]amino]-3-fluoro-N-hydroxy-5-nitro-benzamide;
- 15 18. 2-(2-Chloro-4-iodo-phenylamino)-3,5-difluoro-N-hydroxy-4-phenylamino-benzamide;
19. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-N-hydroxy-5-nitro-4-(3-sulfamoyl-phenylamino)-benzamide;
20. 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-N-hydroxy-5-nitro-4-(2-sulfamoyl-phenylamino)-benzamide;
- 20 21. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3-fluoro-5-nitro-4-(4-sulfamoyl-phenylamino)-benzamide;
22. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3-fluoro-5-nitro-4-phenylamino-benzamide;
- 25 23. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3-fluoro-5-nitro-4-phenoxy-benzamide;
24. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3-fluoro-5-nitro-4-phenylsulfanyl-benzamide;
25. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3-fluoro-4-(methyl-phenyl-amino)-5-nitro-benzamide;
- 30 26. 2-[(2-chloro-4-iodophenyl)amino]-3-fluoro-N-cyclopropylmethoxy-4-[[4-[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-5-nitro-benzamide;

27. 2-[(2-chloro-4-iodophenyl)amino]-4-[[4-[(dimethylamino)carbonyl]phenyl]-  
amino]-3-fluoro-N-cyclopropylmethoxy-5-nitro-benzamide;
28. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,5-difluoro-4-  
phenylamino-benzamide;
- 5 29. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3-fluoro-5-  
nitro-4-(3-sulfamoyl-phenylamino)-benzamide; and
30. 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3-fluoro-5-nitro-4-  
(2-sulfamoyl-phenylamino)-benzamide.

10 In the scheme below, W can also be any of the values described herein for  
formula (I)A or (II)A in the section describing preferred values for W. The  
compound numbers provided in the scheme correspond to the numbers provided  
in the above list; these compounds are illustrative, not limitative, of the invention.

## FORMULAE (I)A AND (II)A EXAMPLES



A third aspect of the invention features the use of compounds shown in formula (I)B in the Summary section. Embodiments of the invention include compounds wherein: (a)  $R_C$  is  $C_{1-2}$  alkyl; (b)  $W$  is OH, or  $W$  is  $NHOR_1$  (c)  $R_{10}$  is methyl or chloro; (d)  $R_{11}$  is fluoro; (e)  $R_{11}$  is H; (f)  $J$  is trihalomethyl or methylthio; (g)  $J$  is  $SO_2CH_3$ ; (h)  $J$  is  $SOCH_3$ ; (i)  $J$  is  $C_{3-8}$  alkynyl where the triple bond is between the carbon atoms alpha and beta to the phenyl group; (j)  $R_1$  has at least one hydroxy substituent; (k)  $R_1$  is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenethyl, allyl,  $C_{3-5}$  alkenyl,  $C_{3-5}$  alkynyl,  $C_{3-6}$  cycloalkyl, ( $C_{3-5}$  cycloalkyl) $C_{1-2}$  alkyl, or ( $C_{3-5}$  heterocyclic radical) $C_{1-2}$  alkyl; (l)  $R_1$  is H or ( $C_{3-4}$  cycloalkyl) $C_{1-2}$  alkyl; (m)  $R_2$  is H, methyl,  $C_{3-4}$  alkynyl,  $C_{3-5}$  cycloalkyl, or ( $C_{3-5}$  cycloalkyl)methyl; (n)  $R_A$  is H, methyl, ethyl, isobutyl, hydroxyethyl, hydroxypropyl, cyclopropylmethyl, cyclobutylmethyl,  $C_{3-4}$  alkynyl, phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxy-propyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and  $R_B$  is H; or where  $R_B$  is methyl and  $R_A$  is phenyl; (o) each of  $R_4$  and  $R_6$  is H, and  $R_5$  is F; (p) each of  $R_4$ ,  $R_5$ , and  $R_6$  is F; (q)  $R_5$  is F; (r) each  $R_5$  and  $R_6$  is F and  $R_6$  is Br; (s) each  $R_5$  and  $R_6$  is F and  $R_6$  is H; (t)  $J$  is 1,2,5-thiadiazol-3-yl; or a combination thereof.

Preferably, where one of  $R_1$ ,  $R_2$ ,  $R_A$ ,  $R_B$ ,  $R_C$ ,  $R_D$ ,  $R_E$ ,  $R_F$ , and  $R_G$ , for example, is an alkenyl or alkynyl group, its double or triple bond, respectively, is not adjacent the point of attachment. For example, where  $W$  is  $NR_2OR_1$ ,  $R_2$  is preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

Examples of compounds of formula (I)B include: 4-fluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 2-(4-methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-

methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methane-sulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; and 2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzoic acid; and the corresponding hydroxamic acid or cyclopropylhydroxamic acid of each.

Preferred examples of compounds of formula (I)B are : 4-Fluoro-2-(4-methanesulfanyl-phenylamino)-benzoic acid (1); 4-Fluoro-2-(4-methanesulfinyl-phenylamino)-benzoic acid (2); 4-Fluoro-2-(4-methanesulfonyl-phenylamino)-benzoic acid (3); 4-Fluoro-2-(2-methyl-4-trimethylsilanylethynyl-phenylamino)-benzoic acid (6); 4-Fluoro-2-(2-methyl-4-ethynyl-phenylamino)-benzoic acid (7). Biological data on these seven compounds is given on page 17; full characterization of the compounds - MP, NMR, MS, IR and CHN- is given on pages 28-31.

Additional preferred compounds include the following: (a) 5-Bromo-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 5-Bromo-N-cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzamide; (b) 5-Bromo-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzamide; 2-(4-Ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4,5-trifluoro-benzamide; 2-(4-Ethynyl-Cl-methyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 5-Bromo-N-cyclopropylmethoxy-2-(4-ethynyl-Cl-methyl-phenylamino)-3,4-difluoro-benzamide; (c) 5-bromo-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-



methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; (d) 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; (e) N-cyclopropylmethoxy-3,4-difluoro-2-(4-imidazol-1-yl-2-methyl-phenylamino)-benzamide; (f) N-cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-[1,2,5]thiadiazol-3-yl-phenylamino)-benzamide; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-3,4,5-trifluoro-benzoic acid; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; (g) 2-[4-[4-(2-dimethylamino-ethoxy)-[1,2,5]thiadiazol-3-yl]-2-methyl-phenylamino]-3,4,5-trifluoro-benzoic acid; (h) N-cyclopropylmethoxy-3,4,5-trifluoro-2-[2-methyl-4-[4-(2-piperidin-1-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino]-benzamide.

Further preferred compounds include: (a) 5-bromo-2-(2-chloro-4-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-chloro-4-methanesulfinyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 2-(2-chloro-4-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid; 5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4-difluoro-benzoic acid; (b) 5-bromo-2-(2-chloro-4-methylsulfanyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methylsulfanyl-

- phenylamino)- N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-phenylamino)- N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methylsulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; and (c) 2-[2-chloro-4-(3H-imidazol-1-yl)-phenylamino]-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-[1,2,5]thiadiazol-3-yl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-[4-(2-chloro-4-chloro-[1,2,5]thiadiazol-3-yl)-phenylamino]-3,4,5-trifluoro-benzoic acid; 2-[2-chloro-4-(4-chloro-[1,2,5]thiadiazol-3-yl)-phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-{4-[4-(2-dimethylamino-ethoxy)-[1,2,5]thiadiazol-3-yl]-2-methyl-phenylamino}-3,4,5-trifluoro-benzoic acid; 2-{2-chloro-4-[4-(2-piperidin-1-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino}-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;
- Additional preferred compounds include: (a) 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 5-Bromo-2-(2-chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-N-hydroxy-3,4,5-trifluoro- benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(4-Ethynyl-2-chloro-phenylamino)-4-nitro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-Cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-phenylamino)- 4-fluoro-N-hydroxy-benzamide; 5-Bromo-2-(4-ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; (b) 2-(2-Chloro-4-ethynyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-fluoro-benzamide; 5-Bromo-2-(2-chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-N-hydroxy-4-nitro-benzamide; and (c) 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-fluoro-benzamide; 2-(2-Chloro-4-

methanesulfinyl-phenylamino)- 4-fluoro-N-hydroxy-benzamide; 2-(2-chloro-4-imidazol-1-yl-phenylamino)- 3,4-Difluoro-benzoic acid.

A fourth aspect of the invention features the use of compounds shown in formula (I)C in the Summary section.

Examples of compounds of formula (I)C have structures wherein:

- (a) the sulfamoyl group is *meta* to W(CO)- and *para* to the bridging NH; (b) the sulfamoyl group is *para* to W(CO)- and *meta* to the bridging NH; (c) R<sub>4</sub> is fluoro;
- (d) R<sub>3</sub> is fluoro; (e) R<sub>3</sub> is H; (f) W is OH; (g) W is NR<sub>2</sub>OR<sub>1</sub>; (h) each of R<sub>3</sub> and R<sub>4</sub> is fluoro; (i) R<sub>1</sub> has at least one hydroxy substituent; (k) R<sub>1</sub> is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenethyl, allyl, C<sub>2-5</sub> alkenyl, C<sub>2-5</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, (C<sub>3-5</sub> cycloalkyl)C<sub>1-2</sub> alkyl, (C<sub>3-5</sub> heterocyclic radical)-C<sub>1-2</sub> alkyl, or (CH<sub>2</sub>)<sub>2-4</sub>NR<sub>A</sub>R<sub>B</sub>; (l) R<sub>1</sub> is H or (C<sub>3-4</sub> cycloalkyl)C<sub>1-2</sub> alkyl; (m) R<sub>2</sub> is H, methyl, C<sub>2-4</sub> alkynyl, C<sub>3-5</sub> cycloalkyl, or (C<sub>3-5</sub> cycloalkyl)methyl; (n) R<sub>A</sub> is H, methyl, ethyl, isobutyl, hydroxyethyl, hydroxypropyl, cyclopropylmethyl, cyclobutylmethyl, C<sub>3-4</sub> alkynyl, phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxypropyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and R<sub>B</sub> is H; or where R<sub>B</sub> is methyl and R<sub>A</sub> is phenyl; (o) R<sub>7</sub> is (CH<sub>2</sub>)<sub>2-4</sub>(NR<sub>C</sub>R<sub>D</sub>); (p) NR<sub>C</sub>R<sub>D</sub> is selected from morpholinyl, piperazinyl, pyrrolidinyl, or piperadinyl; (q) R<sub>C</sub> is methyl, ethyl, hydroxyethyl, or hydroxypropyl; (r) R<sub>5</sub> is methyl or chloro; (s) R<sub>D</sub> is methyl, ethyl, hydroxyethyl, or hydroxypropyl; (t) or combinations thereof, such as wherein each of R<sub>C</sub> and R<sub>D</sub> is methyl or ethyl.

Preferably, where one of R<sub>1</sub>, R<sub>2</sub>, R<sub>A</sub>, R<sub>B</sub>, R<sub>C</sub>, or R<sub>D</sub> is an alkenyl or alkynyl group, the double or triple bond, respectively, is not adjacent the point of attachment. For example, where W is NR<sub>2</sub>OR<sub>1</sub>, R<sub>2</sub> is preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

Examples of compounds of formula (I)C include: 2-(2-chloro-4-iodo-phenylamino)-4-sulfamoyl-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-4-(2-morpholin-4-yl-ethylsulfamoyl)-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-

phenylamino)-N-cyclopropylmethoxy-4-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-sulfamoyl-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-5-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(2-morpholin-4-yl-ethylsulfamoyl)-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-5-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide; and 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide.

Other examples include 5-[bis-(4-methoxy-benzyl)-sulfamoyl]-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid; and 2-(2-chloro-4-iodo-phenylamino)-5-dimethylsulfamoyl-3,4-difluoro-benzoic acid methyl ester.

Additional examples include 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-phenylamino)-benzoic acid; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; N-cyclopropylmethoxy-5-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-5-(ethyl-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-phenylamino)-benzoic acid; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-pyridin-2-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-[(pyridin-2-ylmethyl)-sulfamoyl]-benzamide; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; N-cyclopropylmethoxy-5-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-5-(ethyl-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(methyl-pyridin-2-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-[(pyridin-2-ylmethyl)-sulfamoyl]-benzamide; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid, 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-5-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-3-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-5-(ethyl-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-3-ylmethyl-sulfamoyl]-benzamide; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-

cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-pyridin-2-ylmethyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-2-ylmethyl)-sulfamoyl]-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-2-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; 5-(benzyl-pyridin-2-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-[(pyridin-4-ylmethyl)-sulfamoyl]-benzamide; N-cyclopropylmethoxy-5-(ethyl-pyridin-4-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-pyridin-4-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-phenyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-phenylsulfamoyl-benzamide; N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(pyridin-3-ylsulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-2-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; 5-(benzyl-pyridin-2-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-[(pyridin-4-ylmethyl)-sulfamoyl]-benzamide; N-cyclopropylmethoxy-5-(ethyl-pyridin-4-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(methyl-pyridin-4-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-

phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(methyl-phenyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-phenylsulfamoyl-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(pyridin-3-ylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-2-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-benzamide; 5-(benzyl-pyridin-2-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-4-ylmethyl)-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-5-(ethyl-pyridin-4-ylmethyl-sulfamoyl)-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-pyridin-4-ylmethyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-4-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-phenyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-phenylsulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(pyridin-3-ylsulfamoyl)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-phenylsulfamoyl-benzamide; N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-(pyridin-3-ylsulfamoyl)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 4-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-4-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; -cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-4-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-phenylsulfamoyl-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-methyl-

phenylamino)-4-(pyridin-3-ylsulfamoyl)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 4-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-4-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-4-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-phenylsulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-(pyridin-3-ylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 4-(bis-pyridin-3-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; and 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-benzamide.

Further examples include: PD 298469, 2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-methoxy-5-(4-methyl-piperazine-1-sulfonyl)-benzamide; PD 298470, 2-(2-Chloro-4-iodo-phenylamino)-5-[(2-diethylamino-ethyl)-methyl-sulfamoyl]-3,4-difluoro-N-methoxy-benzamide; PD 298450, 2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-methoxy-5-(methyl-prop-2-ynyl-sulfamoyl)-benzamide; PD 298451, 1-[4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-methoxycarbamoyl-benzenesulfonyl]-piperidine-3-carboxylic acid amide; PD 298452, 2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-methoxy-5-[methyl-(2-pyridin-2-yl-ethyl)-sulfamoyl]-benzamide; PD 298453, 2-(2-Chloro-4-iodo-phenylamino)-5-[(3-dimethylamino-propyl)-methyl-sulfamoyl]-3,4-difluoro-N-methoxy-benzamide; PD 298454, 2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-methoxy-5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-benzamide; PD 298455, 5-[Bis-(2-methoxy-ethyl)-sulfamoyl]-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-



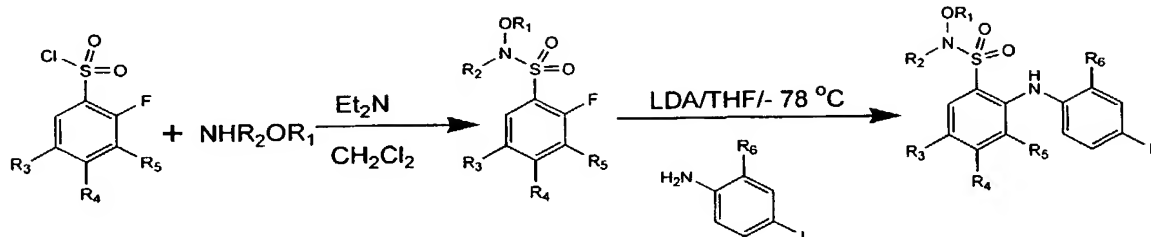
methoxy-benzamide; PD 298456, 5-[Benzyl-(2-dimethylamino-ethyl)-sulfamoyl]-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-methoxy-benzamide; and PD 298457, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-5-dimethylsulfamoyl-3,4-difluoro-benzamide; PD 298461, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(methyl-prop-2-ynyl-sulfamoyl)-benzamide; PD 298462, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-[4-(4-fluoro-phenyl)-piperazine-1-sulfonyl]-benzamide; PD 298466, N-Allyloxy-5-[benzyl-(2-dimethylamino-ethyl)-sulfamoyl]-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzamide; PD 298468, 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(4-methyl-piperazine-1-sulfonyl)-benzamide; and PD 298449, 2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-5-(methoxy-methyl-sulfamoyl)-N-(2-morpholin-4-yl-ethoxy)-benzamide.

Particularly preferred compounds include: PD 298458, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(4-methyl-piperazine-1-sulfonyl)-benzamide; PD 298459, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(methyl-phenyl-sulfamoyl)-benzamide; PD 298460, 5-(Allyl-methyl-sulfamoyl)-N-allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzamide; PD 298463, 1-[5-Allyloxycarbamoyl-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonyl]-piperidine-3-carboxylic acid amide; PD 298464, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-5-[(3-dimethylamino-propyl)-methyl-sulfamoyl]-3,4-difluoro-benzamide; PD 298465, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-benzamide; and PD 298467, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(methoxy-methyl-sulfamoyl)-benzamide.

## C. Synthesis

The disclosed compounds can be synthesized according to Scheme 1 below.

5



One equivalent of appropriately substituted sulfonyl chloride is added to a solution of one equivalent of appropriately substituted hydroxylamine and excess triethylamine in CH<sub>2</sub>Cl<sub>2</sub> or Et<sub>2</sub>O and stirred for 30 minutes. The triethylamine hydrochloride precipitate is separated by filtration and discarded. If necessary, the product is further purified by chromatography on silica column. The pure 2-fluor hydroxamic or hydroxamate product is then added to a solution of appropriately substituted lithium anilide prepared by adding LDA to the aniline in THF at -78 °C. After stirring at room temperature for 16 hours, the reaction mixture is poured in to Et<sub>2</sub>O-HCl. Any precipitated solid is separated by filtration and discarded. The filtrate is concentrated and the resulting crude product is purified on silica column to give the desired target product.

The disclosed compounds can also be made by other synthetic organic methods, as well as automated or combinatorial methods.

The disclosed compounds can be synthesized according to the following two Schemes, or variants thereof (see also Example 1A).

Regarding the first step of synthetic Scheme 1A, the reaction of the aniline  
5 and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of the aniline in an unreactive organic solvent such as tetrahydrofuran, or toluene, in the presence of a base such as lithium diisopropylamide, lithium hexamethyldisilazide, n-butyl lithium, sodium hydride, or sodium amide. The reaction generally is carried out at a temperature  
10 of about  $-78^{\circ}\text{C}$  to about  $25^{\circ}\text{C}$ , and normally is complete within 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

Turning to the second step, the 2-phenylamino benzoic acid derivative is  
15 next reacted with an equimolar quantity or excess of a nucleophile such as an aniline, a phenol, or a thiophenol by mixing in an unreactive organic solvent such as tetrahydrofuran, or toluene, in the presence of a base such as lithium diisopropylamide, lithium hexamethyldisilazide, n-butyl lithium, sodium hydride, or sodium amide. The reaction generally is carried out at a temperature of about  $-$   
20  $78^{\circ}\text{C}$  to boiling, and normally is complete within 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

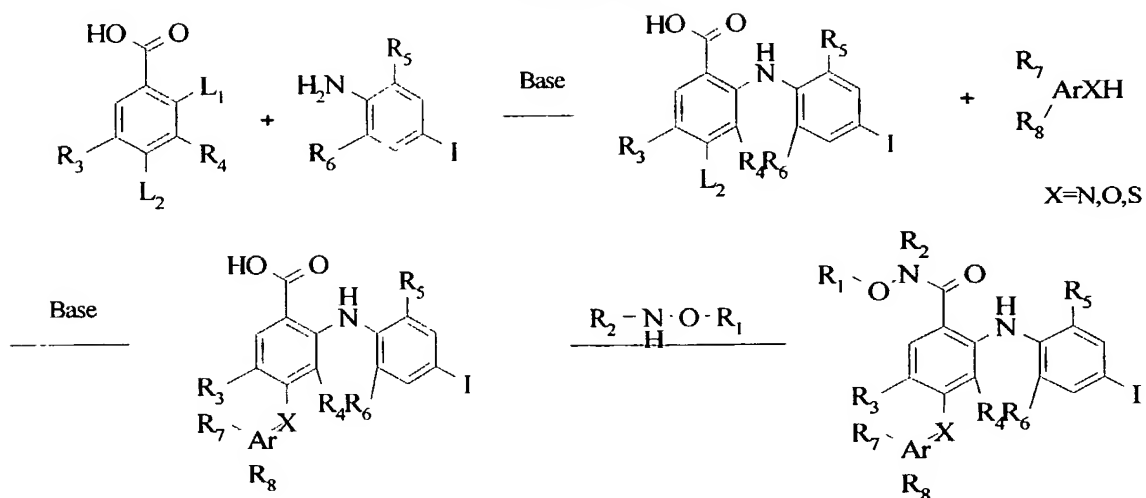
Finally, regarding step 3, the 4-arylheteroatom-2-phenylamino benzoic  
25 acid derivative next is reacted with a nucleophile such as ammonia, an amine, an alcohol, hydrazine, a hydrazine derivative, or a hydroxylamine derivative in the presence of a peptide coupling reagent. Amines that can be employed include monomethylamine and aniline. Alcohols that can be employed include cyclobutylmethanol and phenol. Hydrazine derivatives that can be employed  
30 include N,N-dimethylhydrazine and 1-aminopiperidine. Hydroxylamine derivatives that can be employed include methoxylamine, N-ethyl-isopropoxy amine, and tetrahydrooxazine. Typical coupling reagents include 2-ethoxy-1-

ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris-(pyrrolidino)-phosphonium hexafluorophosphate (PyBrOP) and (benzotriazolyloxy) tripyrrolidino phosphonium hexafluorophosphate (PyBOP).

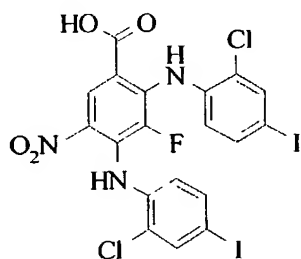
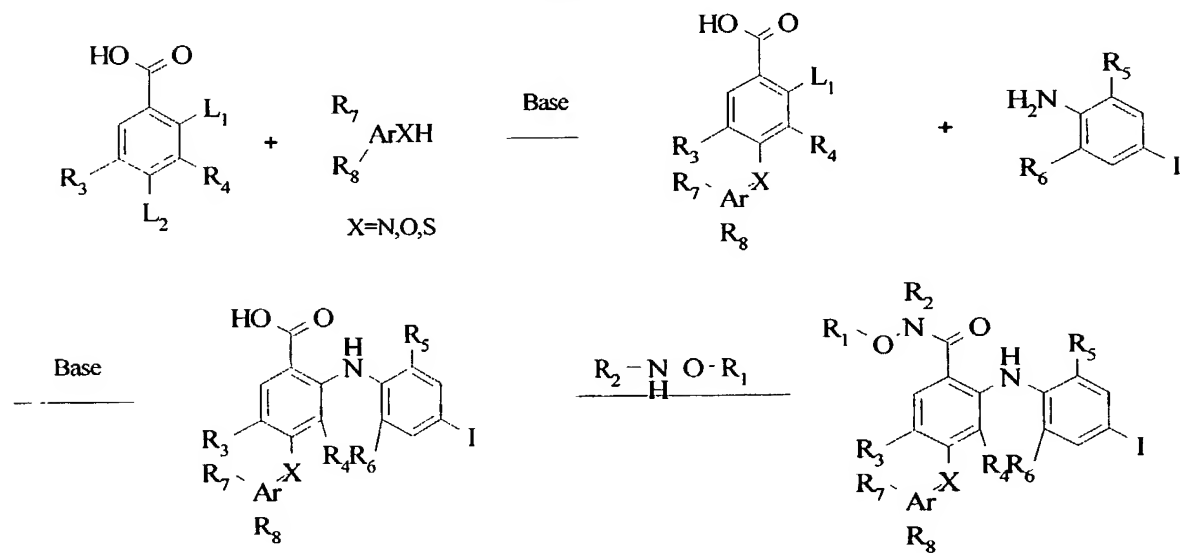
The 4-arylheteroatom-2-phenylamino benzoic acid derivative and the nucleophile  
5 normally are mixed in approximately equimolar quantities in an unreactive solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to  
10 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone diethyl ether or ethanol.

Referring to synthetic Scheme 2A, an alternative method for making the  
15 compounds of the invention involves first coupling the benzoic acid derivative with the arylheteroatom nucleophile, and then reacting this 4-arylheteroatom benzoic acid derivative with an aniline. The final step involves the coupling of the 4-arylheteroatom-2-phenylamino benzoic acid derivative with the ammonia, amine, alcohol, hydrazine, hydrazine derivative, or hydroxylamine derivative with  
20 a peptide coupling reagent. The general reaction conditions for all of the steps in Scheme 2A are similar to those described above for synthetic Scheme 1A.

## Scheme 1A



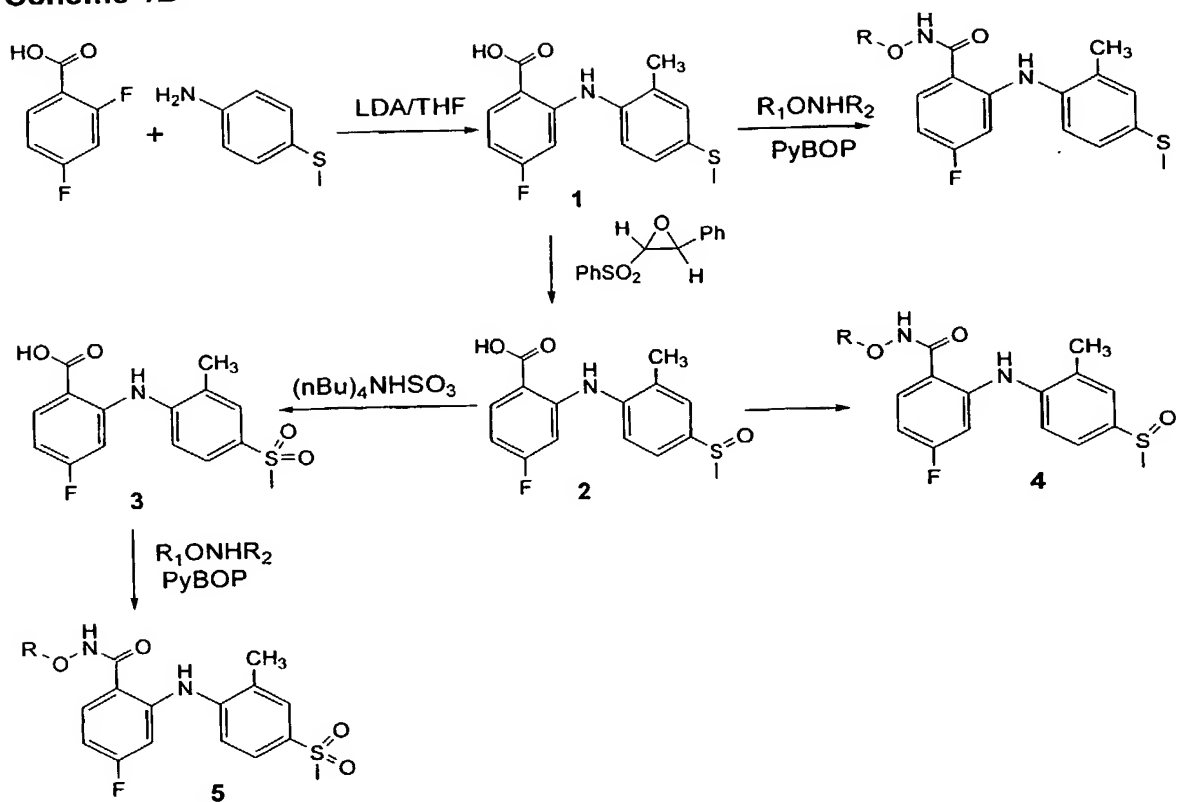
## Scheme 2A



PD 195928  
APK IC<sub>50</sub>=30±8 nM

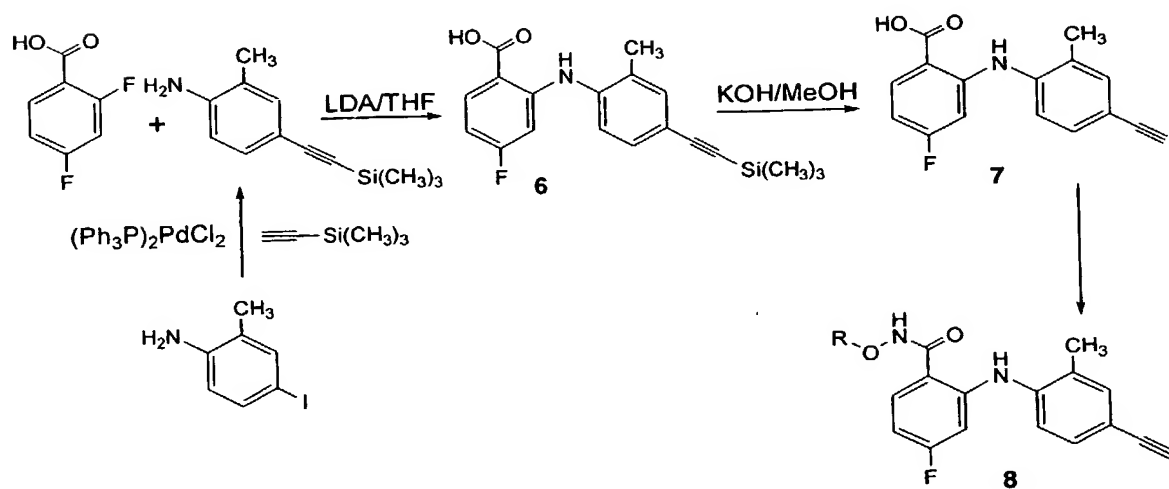
The disclosed compounds can be synthesized according to the following five schemes, or variants thereof. The abbreviation PyBOP is (benzotriazolyl-oxy)-tripyrrolidino phosphonium hexafluorophosphate. These synthetic strategies  
5 are further exemplified in Examples 1B-5B below:

## Scheme 1B

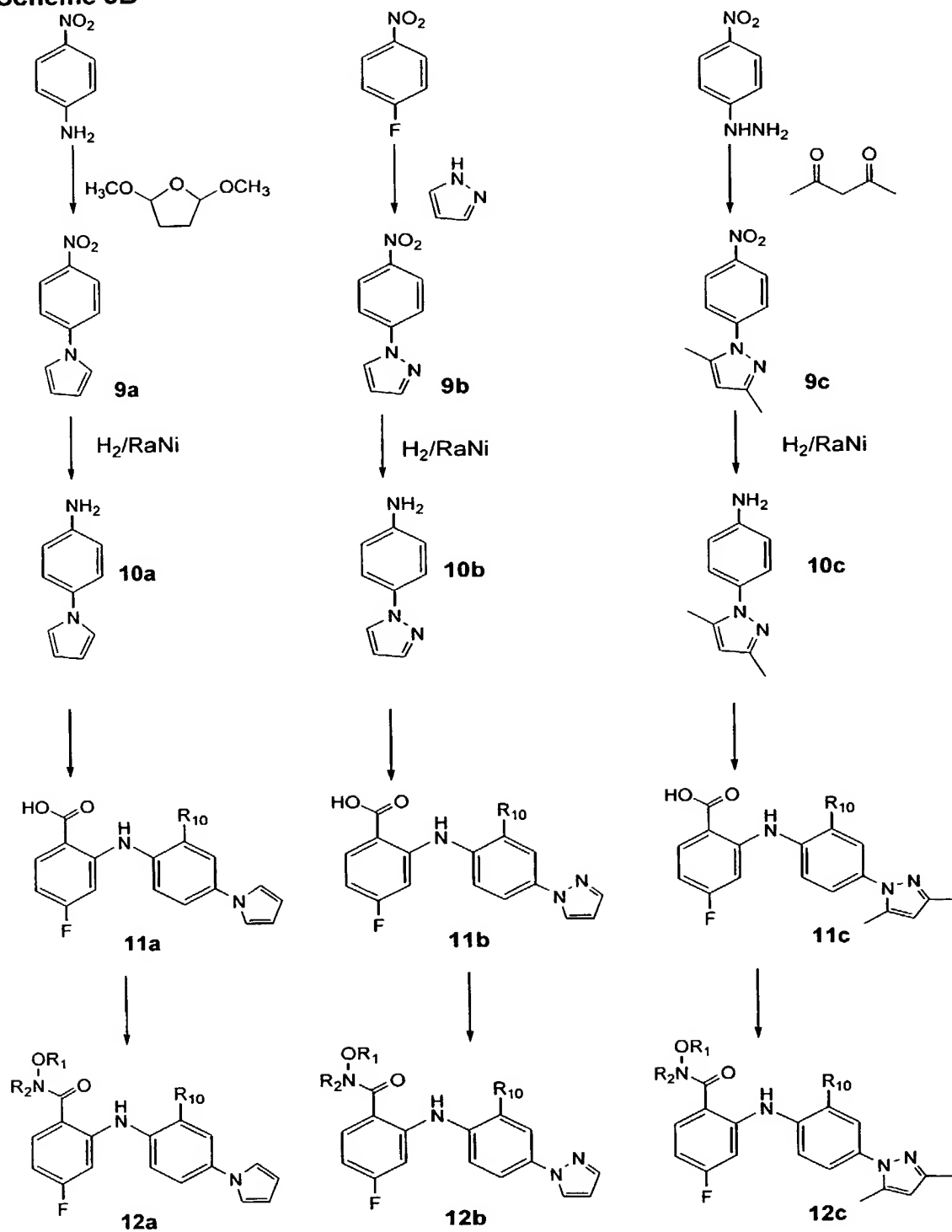


## Scheme 2B

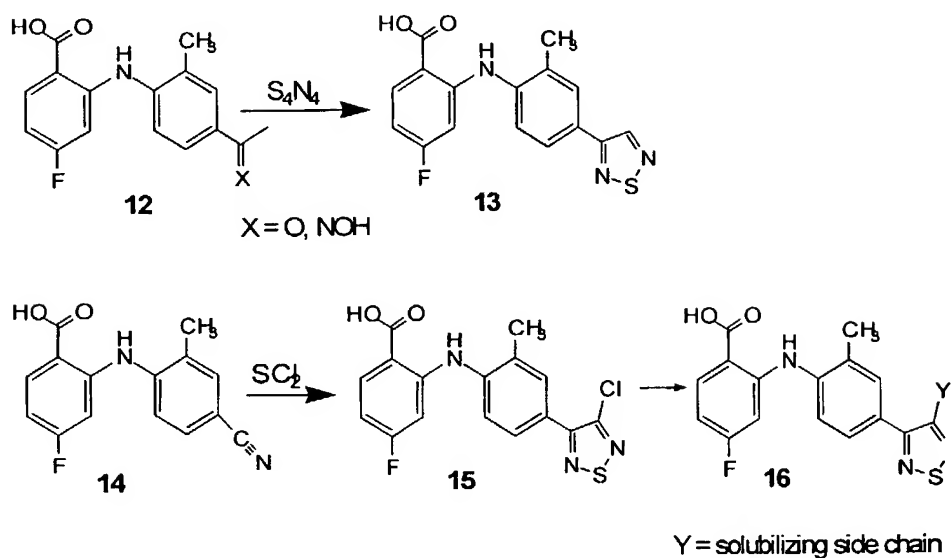
5



## Scheme 3B



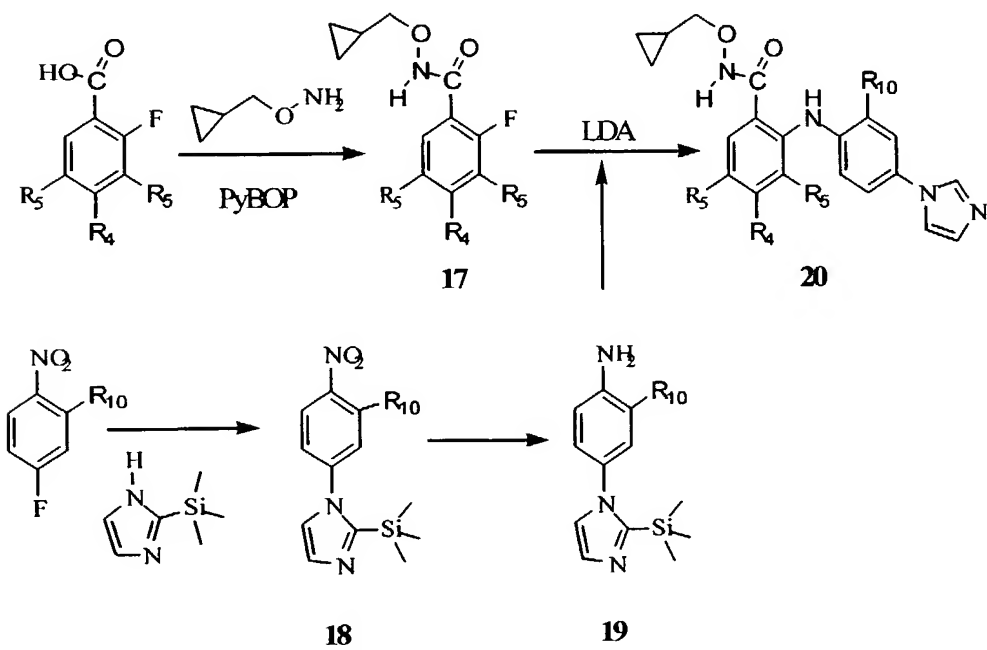


**Scheme 4B** 3-Aryl-1,2,5-thiadiazols

5

**Scheme 5B**

10



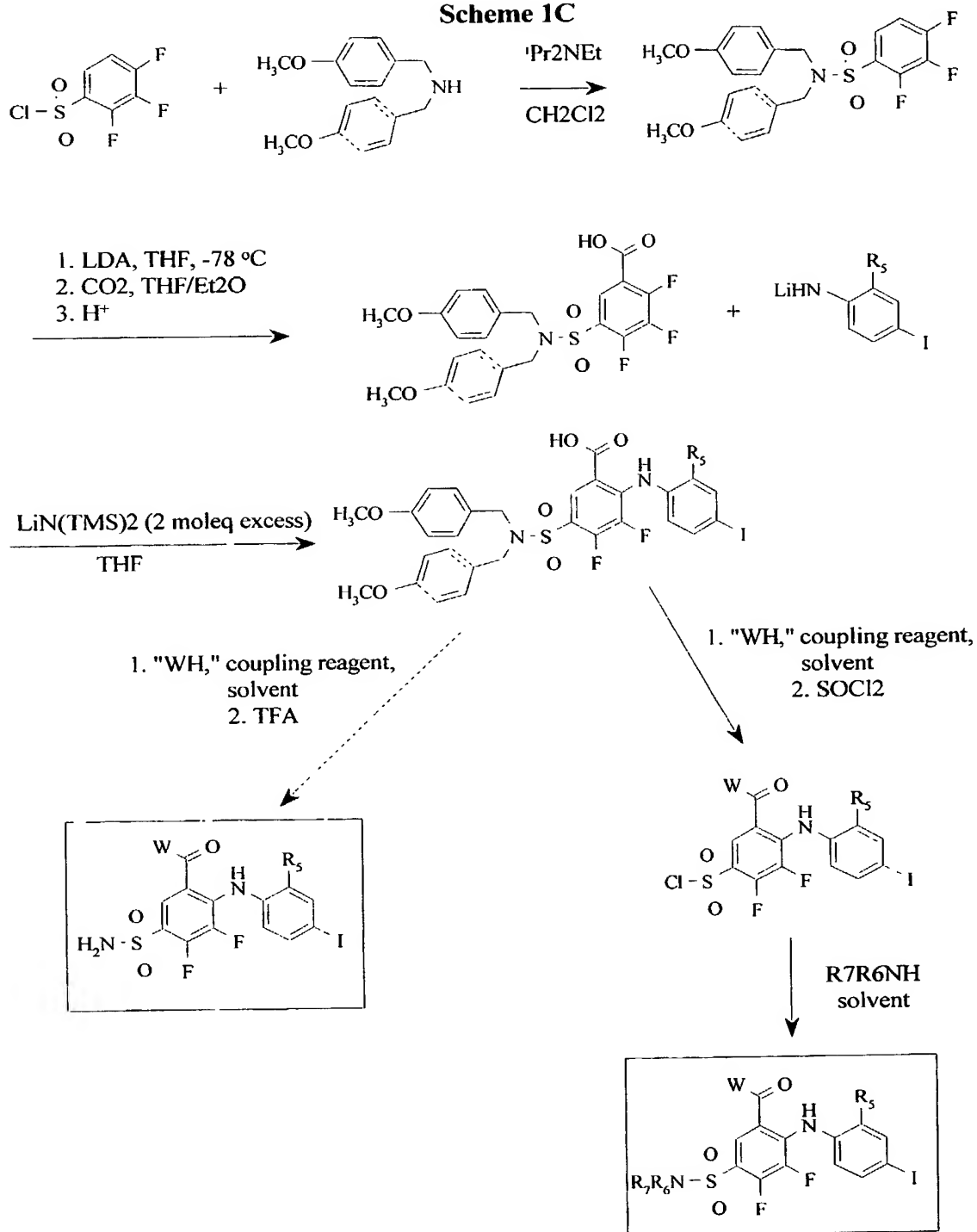
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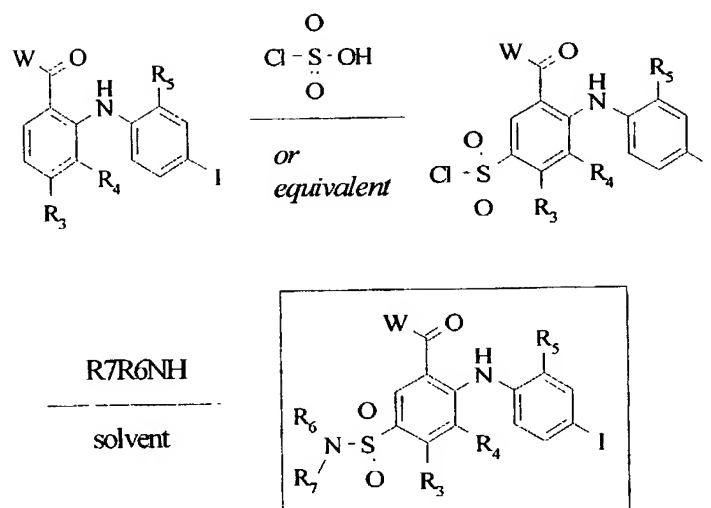
The disclosed compounds can be synthesized according to the following four Schemes, or variants thereof. These synthetic strategies, which are suitable for conventional or combinatorial synthetic methods, are further exemplified in Examples 1C-4C below.

5

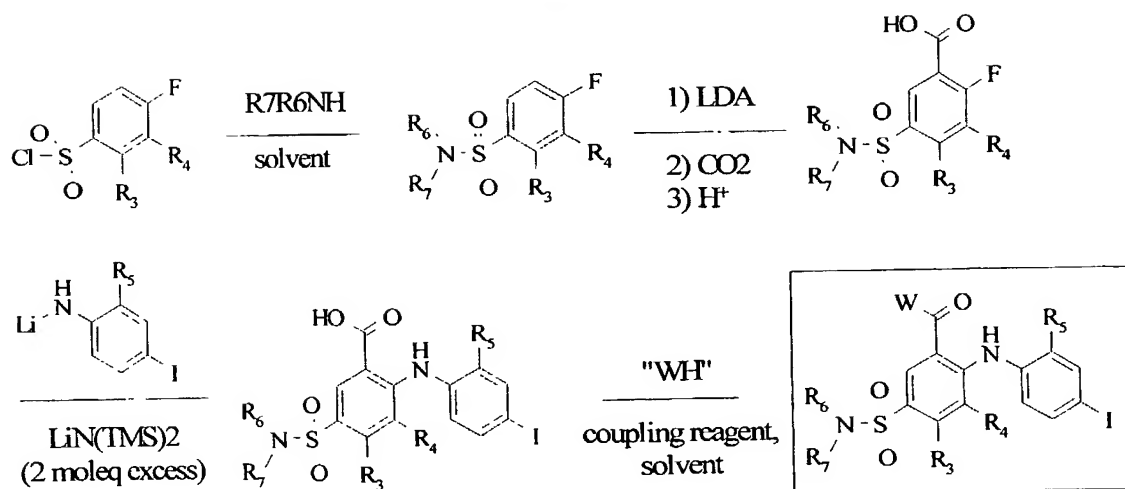
## Scheme 1C



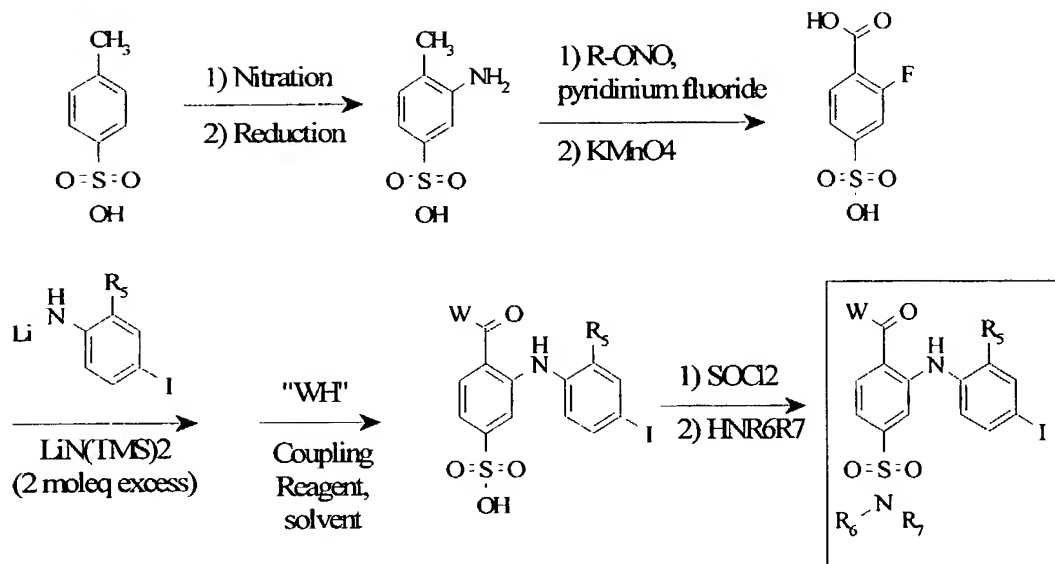
## Scheme 2C



## Scheme 3C



## Scheme 4C



Amine reagents such as  $R_6R_7NH$  in the schemes above are either commercially available or through straightforward modification of commercially available intermediates. Examples of such amine reagents, which can be reacted with the appropriate intermediate in a combinatorial or matrix method, are provided below.

- 5 For example, in section B (Compounds), starting at page 8, line 16, there are three sets of thirty (one set each for  $R_5 = H, Me,$  and  $Cl$ ). The table below provides a number (corresponding to order that the name is found in the text; for example, "1" corresponds to compounds 1, 31, and 61 in the list of 90 compounds); the amine reagent name; and a Chemical Abstracts number.
- 10 Where a PD number is listed, the amine reagent was prepared from commercially available starting materials.

Number (position in subset of 30)	Amine reagent name	CAS # or PD #
1	3,3'-dipicolylamine	1656-94-6
2	3,3'-dipicolylamine	1656-94-6
3	3-(methylaminomethyl)pyridine	20173-04-0
4	3-(aminomethyl)pyridine	3731-52-0
5	"N-(3-diethylaminopropyl)-N-(pyridin-3-ylmethyl)amine"	PD 0096419
6	3-(3-pyridylmethylamino)-1-propanol	6951-00-4
7	3-(ethylaminomethyl)pyridine	PD 0133573
8	2-(3-pyridylmethylamino)ethanol hydrochloride	PD 0018185-0002
9	di-(2-picolyl)amine	1539-42-0
10	di-(2-picolyl)amine	1539-42-0
11	2-(methylaminomethyl)pyridine	PD 0091430
12	2-(aminomethyl)pyridine	3731-51-9
13	3-(2-pyridylmethylamino)-1-propanol	6950-99-8
14	2-(2-pyridylmethylamino)ethanol	PD 0018354
15	2-(N-benzylaminomethyl)pyridine	PD 0054372
16	4-(aminomethyl)pyridine	3731-53-1
17	4-(ethylaminomethyl)pyridine	33403-97-3
18	4-(methylaminomethyl)pyridine	PD 0111199
19	3-(4-pyridylmethylamino)-1-propanol	7251-62-9
20	2-(4-pyridylmethylamino)ethanol hydrochloride	PD 0018008-0002
21	N-methylaniline	100-61-8
22	aniline	62-53-3
23	3-aminopyridine	462-08-8
24	aniline	62-53-3
25	3-aminopyridine	462-08-8
26	3-(aminomethyl)pyridine	3731-52-0
27	3,3'-dipicolylamine	1656-94-6
28	2-(4-pyridylmethylamino)ethanol hydrochloride	PD 0018008-0002
29	3-(methylaminomethyl)pyridine	20173-04-0
30	"N-(3-diethylaminopropyl)-N-(pyridin-3-ylmethyl)amine"	PD 0096419

Additional compounds within claim 1 can be made with the following amine reagents. The corresponding CAS number is provided.

5	2-(methylamino)pyridine	4597-87-9
	2-benzylaminopyridine	6935-27-9
	2-allylaminopyridine	5866-28-4
	2,2'-dipyridylamine	1202-34-2
	2-anilinopyridine	6631-37-4
10	2-aminopyridine	504-29-0
	4-aminopyridine	504-24-5
	2-benzylaminopyridine	6935-27-9
	2-(4-methoxybenzyl)aminopyridine	52818-63-0
15	2-methylaminopyridine	4597-87-9

### Combinatorial Synthesis

The following stock solutions were prepared:

- 1) An acetonitrile (anhydrous) stock solution 0.05 M in 5-chlorosulfonyl-2,3,4-trifluoro-benzoyl chloride.
- 2) Acetonitrile (anhydrous) stock solutions 0.05 M in each of the four appropriate hydroxylamine hydrochlorides (see list A) and 0.3 M in 2,6-lutidine.
- 3) Acetonitrile stock solutions 0.05 M in each of the 25 appropriate amines (see list B). Note that amine salts that were not soluble were also 0.1 M in 2,6-lutidine.
- 4) Acetonitrile (anhydrous) stock solutions in each of the 3 appropriate anilines (see list C) and 0.88 M in lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran).

An array which treated 4 hydroxylamine hydrochlorides independently with 5-chlorosulfonyl-2,3,4-trifluoro-benzoyl chloride, 25 amines, and 1 aniline was prepared to yield a total of 100 reactions. A liquid handling robot was used to transfer the reagents in such a manner as to insure that all possible combinations were achieved. The appropriate hydroxylamine hydrochloride solution (0.05 mmol, 1 mL) was added to a 2-dram vial, and each vial was treated with 5-chlorosulfonyl-2,3,4-trifluoro-benzoyl chloride solution (0.05 mmol, 1 mL). After

20 minutes the appropriate amine solution (0.05 mmol, 1 mL) was added sequentially. After a further 20 minutes the vials were treated with the solution of 4-iodoaniline (0.055 mmol, 1 mL). The vials were capped and shaken overnight at room temperature. The reactions were quenched with 1 mL of a 1 M aqueous ammonium chloride solution. The vials were concentrated to dryness under a stream of nitrogen and purified by reverse phase HPLC using a 30x100 mm YMC ODS-A (C18) column. The mobile phase was acetonitrile/water (both with 0.05% trifluoroacetic acid) at 25 mL/min and a linear gradient of 10-100% over 6.5 min and then 3.5 min at 100%, detection was at 214 nm.

10 An array which treated 4 hydroxylamine hydrochlorides independently with 5-chlorosulfonyl-2,3,4-trifluoro-benzoyl chloride, 25 amines, and 1 aniline was prepared to yield a total of 100 reactions. A liquid handling robot was used to transfer the reagents in such a manner as to insure that all possible combinations were achieved. The appropriate hydroxylamine hydrochloride solution (0.05 mmol, 1 mL) was added to a 2-dram vial, and each vial was treated with 5-chlorosulfonyl-2,3,4-trifluoro-benzoyl chloride solution (0.05 mmol, 1 mL). After 20 minutes the appropriate amine solution (0.05 mmol, 1 mL) was added sequentially. After a further 20 minutes the vials were treated with the solution of 4-iodo-2-methylaniline (0.05 mmol, 0.91 mL). The vials were capped and shaken overnight at room temperature. The reactions were quenched with 1 mL of a 1 M aqueous ammonium chloride solution. The vials were concentrated to dryness under a stream of nitrogen and purified by reverse phase HPLC using a 30x100 mm YMC ODS-A (C18) column. The mobile phase was acetonitrile/water (both with 0.05% trifluoroacetic acid) at 25 mL/min and a linear gradient of 10-100% over 6.5 min and then 3.5 min at 100%, detection was at 214 nm.

25 An array which treated 4 hydroxylamine hydrochlorides independently with 5-chlorosulfonyl-2,3,4-trifluoro-benzoyl chloride, 25 amines, and 1 aniline was prepared to yield a total of 100 reactions. A liquid handling robot was used to transfer the reagents in such a manner as to insure that all possible combinations were achieved. The appropriate hydroxylamine hydrochloride solution (0.05 mmol, 1 mL) was added to a 2-dram vial, and each vial was treated with 5-chlorosulfonyl-2,3,4-trifluoro-benzoyl chloride solution (0.05 mmol, 1 mL). After



20 minutes the appropriate amine solution (0.05 mmol, 1 mL) was added sequentially. After a further 20 minutes the vials were treated with the solution of 2-chloro-4-iodoaniline (0.05 mmol, 0.91 mL). The vials were capped and shaken overnight at room temperature. The reactions were quenched with 1 mL of a 1 M aqueous ammonium chloride solution. The vials were concentrated to dryness under a stream of nitrogen and purified by reverse phase HPLC using a 30x100 mm YMC ODS-A (C18) column. The mobile phase was acetonitrile/water (both with 0.05% trifluoroacetic acid) at 25 mL/min and a linear gradient of 10-100% over 6.5 min and then 3.5 min at 100%, detection was at 214 nm.

Combinatorial Synthesis  
Table of Example Reagents

5    List A-Hydroxylamines:

1. O-methyl-hydroxylamine
2. O-allyl-hydroxylamine hydrochloride monohydrate (Aldrich)
3. O-cyclopropylmethyl-hydroxylamine hydrochloride
- 10 4. O-(2-morpholin-4-yl-ethyl)-hydroxylamine hydrochloride

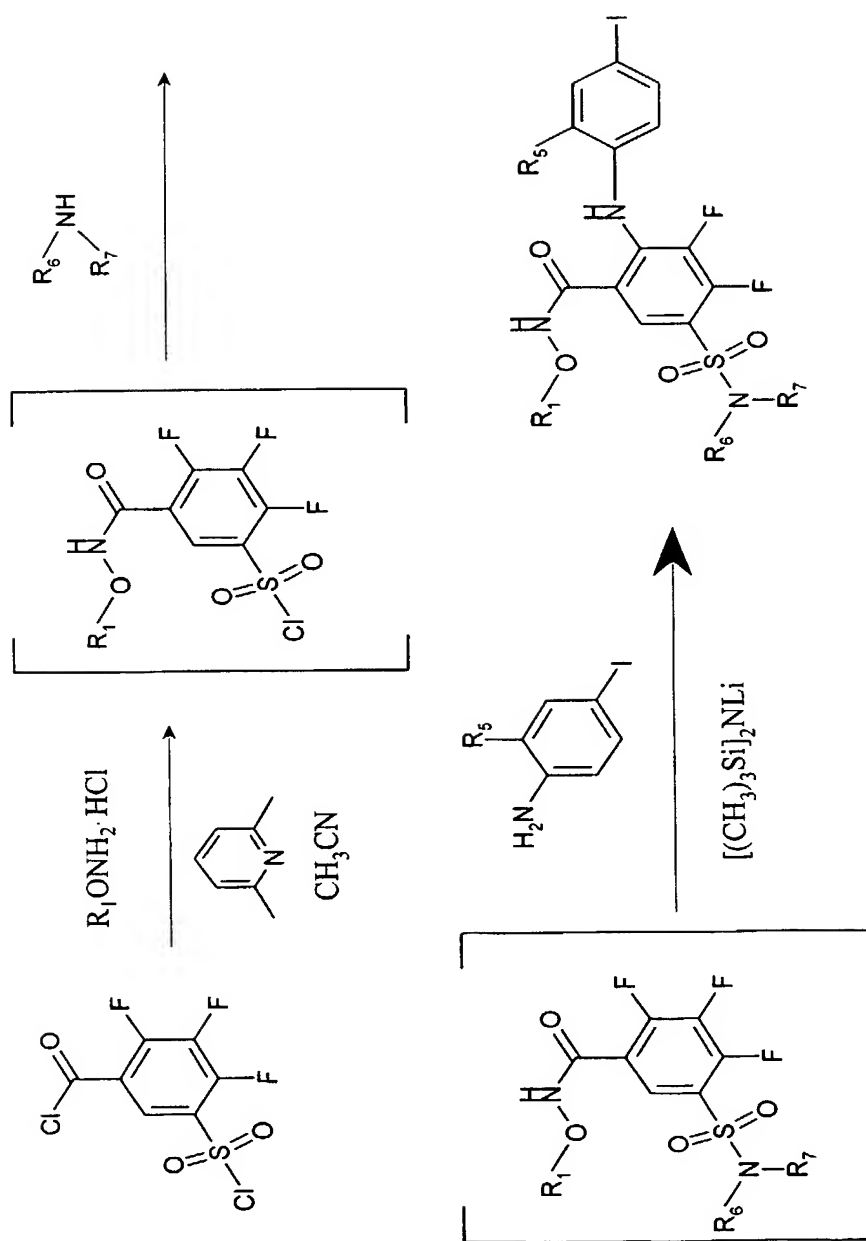
List B-Amines:

1. dimethylamine
- 15 2. diethylamine
3. isopropyl-methyl-amine
4. diisopropylamine
5. methylhydrazine
6. 1-methylpiperazine
- 20 7. *N,N*-diethyl-*N'*-methylethane-1,2-diamine
8. benzylmethylamine
9. dibenzylamine
10. methyl-phenyl-amine
11. allyl-methyl-amine
- 25 12. methyl-prop-2-ynyl-amine
13. methylamino-acetonitrile hydrochloride
14. 1-(4-fluoro-phenyl)-piperazine
15. furan-2-ylmethyl-methyl-amine
16. piperidine-3-carboxylic acid amide
- 30 17. methyl-phenethyl-amine
18. methyl-(2-pyridin-2-yl-ethyl)-amine
19. *N,N,N'*-trimethyl-propane-1,3-diamine
20. methyl-(1-methyl-piperidin-4-yl)-amine
21. 1-pyridin-2-yl-piperazine
- 35 22. bis-(2-methoxy-ethyl)-amine
23. *N'*-benzyl-*N,N*-dimethyl-ethane-1,2-diamine
24. methylamino-acetic acid *tert*-butyl ester hydrochloride
25. *O,N*-dimethyl-hydroxylamine hydrochloride

40

List C-Anilines:

1. 4-iodoaniline
- 45 2. 2-chloro-4-iodoaniline
3. 4-iodo-2-methylaniline



Scheme 5C

## Chemical Examples

5

## Example 1

Preparation of 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide (PD 0297447)

N-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide.

10 To a stirring suspension comprised of O-cyclopropylmethyl-hydroxylamine hydrochloride (5.40 g, 0.0437 mol) in dichloromethane (20 ml) at ambient temperature under a nitrogen atmosphere was added diisopropylethylamine (10.8 ml, 0.062 mol). A solution comprised of 2,3,4-trifluorobenzenesulfonyl chloride (Oakwood Products, Inc., 1.00 g,  $4.34 \times 10^{-3}$  mol) in dichloromethane (120 ml) was added dropwise to the reaction vessel  
15 containing the stirring suspension over a 12 minute period. The reaction mixture was stirred for another 12 minutes and was quenched with 10 % aqueous hydrochloric acid (140 ml). The biphasic mixture was stirred vigorously for 16 hours. The layers were separated and the organic phase  
20 was dried ( $\text{MgSO}_4$ ) and concentrated to 6 ml volume. The concentrated solution was administered to a flash silica column (Biotage, 90 g of silica gel). Elution with dichloromethane afforded 0.8283 g of a white amorphous solid; 68 % yield;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$  signal offset to  $\delta$  7.03; values reported are uncorrected)  $\delta$  7.50 (m, 1H), 7.10 (s, 1H), 6.95 (m, 1H), 3.59 (d, 2H,  $J=7.2$  Hz), 0.80 (m, 1H), 0.31 (m, 2H), 0.02 (m, 2H);  $^{19}\text{F-NMR}$  (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -  
25 122.65 (m, 1F), -129.37 (m, 1F), -156.20 (m, 1F); MS (APCI-) 280 (M-1, 100), 210 (55), 195 (45).

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide (PD 0297447).  
30

To a stirring solution comprised of 2-chloro-4-iodoaniline in tetrahydrofuran (10 ml) at  $-78^\circ\text{C}$  under a nitrogen atmosphere was added a 1.0 M tetrahydrofuran solution of lithium *bis*trimethylsilylamide (6.2 ml, 6.2 x

10<sup>-3</sup> mol) to form a green suspension. The suspension was stirred for five minutes before a stirring suspension comprised of lithiated *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide (prepared by adding 3.0 ml of the 1.0 M lithium *b*is(trimethyl)silylamide solution to a stirring solution  
5 comprised of *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide in 10 ml of tetrahydrofuran at -78 °C under nitrogen gas) was added via canula. The cold bath was removed and the stirring suspension was stirred for one hour. The reaction mixture was quenched with 10 % aqueous hydrochloric acid (50 ml) and the biphasic mixture was concentrated *in vacuo* to an  
10 aqueous suspension that was extracted with diethyl ether (200 ml). The organic phase was dried (MgSO<sub>4</sub>) and was concentrated *in vacuo* to afford a tan oil. The crude product was purified by flash chromatography. Elution with a gradient (hexanes-ethyl acetate 99:1 → (2 min) 9:1 → (25 min) 3:1 afforded 1.10 g of a white amorphous foam; 73 % yield; <sup>1</sup>H-NMR (400 MHz; DMSO) δ  
15 7.69 (m, 1H), 7.59 (d, 1H, J=1.9 Hz), 7.34 (dd, 1H, J=8.7, 1.9 Hz), 7.27 (s, 1H), 7.00 (s, 1H), 6.95 (m, 1H), 6.43 (dd, 1H, J=8.7, 5.8 Hz), 3.52 (d, 2H, J=7.5 Hz), 0.74 (m, 1H), 0.34 (m, 2H), 0.02 (m, 2H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -124.76 (m, 1F), -136.69 (d, 1F, J=18.3 Hz); MS (APCI+) 515 (M+1, 100); (APCI-) 513 (M-1, 50), 443 (73), 428 (100); IR (KBr) 1491 cm<sup>-1</sup>; Anal.  
20 Calcd/found for C<sub>16</sub>H<sub>14</sub>ClF<sub>2</sub>IN<sub>2</sub>O<sub>3</sub>S C, 37.34/36.54; H, 2.74/2.71; N, 5.44/5.15; F, 7.38/7.57.

The APK IC<sub>50</sub> for PD 0297447 is 0.965 μM.

## EXAMPLE 1A

Preparation of 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitrobenzoic acid

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Step a: Preparation of 5-nitro-2,3,4-trifluorobenzoic acid

To gently stirring concentrated sulfuric acid (50 ml) was added fuming nitric acid (3.4 ml, 0.076 mol). Solid 2,3,4-trifluorobenzoic acid (10.00 g, 0.05565 mol) was added directly in increments. After stirring 45 minutes, the reaction mixture had become an orange homogeneous solution which was then poured over chilled water (400 ml). The resulting aqueous suspension was extracted with diethyl ether (3 x 200 ml). The combined extracts were dried with anhydrous magnesium sulfate and concentrated *in vacuo* to yield 12.30 g of a dull, light-yellow solid. Recrystallization from chloroform (50 ml) afforded 9.54 g of the pale yellow microcrystalline product; 78 % yield; m.p. ;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  14.29 (broad s, 1H), 8.43-8.38 (m, 1H);  $^{13}\text{C-NMR}$  (100 MHz; DMSO)  $\delta$  162.41, 154.24 (dd,  $J_{\text{C-F}}=270.1, 10.7$  Hz), 148.35 (dd,  $J_{\text{C-F}}=267.0, 9.2$  Hz), 141.23 (dt,  $J_{\text{C-F}}=253.4$  Hz), 133.95, 123.30 (d,  $J_{\text{C-F}}=2.2$  Hz), 116.92 (dd,  $J_{\text{C-F}}=18.2, 3.8$  Hz);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$  -120.50 to -120.63 (m), -131.133 to -131.27 (m), -153.63 to -153.74 (m).

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Step b: Preparation of 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitrobenzoic acid

To a stirring solution comprised of 2-chloro-4-iodoaniline (Lancaster, 98 %, 12.33 g, 0.04864 mol) in tetrahydrofuran (20 ml) at -78 °C under nitrogen was added a 2.0 M lithium diisopropylamide solution in tetrahydrofuran-heptane-ethylbenzene (Aldrich, 35 ml, 0.070 mol) with a syringe. The addition formed a thick suspension. After five minutes of stirring, a solution comprised of 5-nitro-2,3,4-trifluorobenzoic acid (5.00 g, 0.0226 mol) in tetrahydrofuran (30 ml) was added with a syringe to give a dark reaction mixture. The cold bath was removed and the reaction mixture stirred for 20 minutes. The cool reaction mixture was poured into ether (600 ml) containing an excess of

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hydrogen chloride. The red solution instantly turned to a yellow suspension as a precipitate formed. This precipitate was removed by vacuum filtration. The filtrate was concentrated *in vacuo* to a red powder (10.5 g). The red powder was triturated with boiling chloroform (800 ml). The triturated solids were collected by vacuum filtration to give an orange powder (2.42 g). The mother liquor from the trituration was concentrated *in vacuo* to give a red-orange solid (ca. 10 g undried). This solid was loaded onto a flash silica column. Elution with dichloromethane removed some impurities. Continuing elution with 1 % methanol in dichloromethane afforded ca. 4 g of a red solid. This red solid was dissolved in hot absolute ethanol (100 ml). The solution was boiled down to 50 ml before dilution to 300 ml with hexanes. This solution was boiled to 150 ml and rediluted to 300 ml with hexanes to produce slight turbidity. The mixture was cooled in the refrigerator for three days, affording a yellow precipitate. The precipitate was collected by vacuum filtration and was dried with suction to afford 0.15 g of a yellow solid; 1 % yield; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 8.94 (s, 1H), 8.55 (s, 1H), 7.79 (d, 2H, J=2.0 Hz), 7.61-7.57 (m, 2H), 6.90 (dd, 1H, J=8.5, 3.9 Hz), 6.84 (dd, 1H, J=8.3, 6.6 Hz); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -122.62 (s); MS (APCI+) 692 (6), 691 (8), 690 (31), 689 (10), 688 (55), 171 (47), 130 (100); (APCI-) 691 (4), 690 (12), 689 (14), 688 (70), 687 (32), 686 (100), 506 (50), 453 (97); IR (KBr) 1523 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>19</sub>H<sub>10</sub>Cl<sub>2</sub>Fl<sub>2</sub>N<sub>3</sub>O<sub>4</sub> C, 33.17/33.32; H, 1.47/1.73; N, 6.11/5.73; Cl, 10.31/10.04; F, 2.76/3.70; I, 36.89/34.32.

The APK IC<sub>50</sub> for 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitrobenzoic acid is 29.6 nM.

## EXAMPLE 1B

4-Fluoro-2-(4-methanesulfanyl-phenylamino)-benzoic acid (1).

- 5 To a solution of 4-(methylmercapto)aniline (3.1622 g, 0.02 mole) in THF at  $-78^{\circ}\text{C}$ , a solution of LDA in THF (2M, 30 ml, 0.06 mole) was added and the reaction mixture stirred for 30 minutes at  $-78^{\circ}\text{C}$  (Scheme 1E). Solid 2,4-difluoro benzoic acid (3.1622 g, 0.02 mole) was added and the reaction
- 10 stirred for 16 hours while it warmed up to room temperature. The reaction mixture was poured into ether saturated with HCl gas. HCl gas was bubbled into until precipitation of salts ceased. The precipitated salts were separated by filtration and discarded. The ether layer was concentrated to give **1** as a white solid. Yield 5.63 g (100%); mp  $173-179^{\circ}\text{C}$  (DEC);  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.39 (s, 1H), 8.04 (dd, 1H,  $J=9.2, 6.8$  Hz), 7.32-7.17 (AB quartet, 4H), 6.74 (dd, 1H,  $J=12.1, 2.4$  Hz), 6.46-6.41 (m, 1H), 2.51 (s, 3H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )  $\delta$  172.79, 167.57 (d,  $J_{\text{C-F}}=253.4$  Hz), 151.55 (d,  $J_{\text{C-F}}=12.2$  Hz), 136.83, 135.40 (d,  $J_{\text{C-F}}=12.2$  Hz), 134.72, 128.31, 124.60, 106.51, 105.12 (d,  $J_{\text{C-F}}=22.9$  Hz), 99.79 (d,  $J_{\text{C-F}}=26.7$  Hz), 16.51;  $^{19}\text{F-NMR}$  (376 MHz;  $\text{CDCl}_3$ )
- 20  $\delta$  -101.39 to -101.46 (m); MS (APCI+) 278 ( $\text{M}+1$ , 100); IR (KBr) 3319, 1664, 1589,  $1258\text{ cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{14}\text{H}_{12}\text{FNO}_2\text{S}$  C, 60.64/60.99; H, 4.36/4.63; N, 5.05/4.80; S, 11.56/10.97.

## EXAMPLE 2B

4-Fluoro-2-(4-methanesulfinyl-phenylamino)-benzoic acid (2).

- 25 A mixture of **1** (Scheme 1B) (0.286 g, 0.001031 mole) and oxaziridine (0.235 g, 0.0009 mole) in  $\text{CHCl}_3$  (30 ml) at room temperature for 2 hours. The solvent was removed and the resulting brown oil chromatographed on silica column. Elution with  $\text{CH}_2\text{Cl}_2$  removed fast moving byproduct. Further elution
- 30 with  $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$  (9.5:0.5),  $R_f = 0.27$ , gave pure **2** as a light brown solid. Yield 132.8 mg (50%); mp  $191-192^{\circ}\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.77 (s, 1H), 8.08 (dd, 1H,  $J=8.9, 6.7$  Hz), 7.70-7.39 (AB quartet, 4H), 6.98 (dd, 1H,  $J=11.6, 2.4$  Hz), 6.57-6.52 (m, 1H), 2.80 (s, 3H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )



$\delta$  170.76, 167.18 (d,  $J_{C-F}$ =253.3 Hz), 149.33 (d,  $J_{C-F}$ =12.2 Hz), 143.02, 139.50,  
 135.37 (d,  $J_{C-F}$ =12.2 Hz), 125.47, 122.32, 108.22, 106.35 (d,  $J_{C-F}$ =22.8 Hz),  
 100.69, (d,  $J_{C-F}$ =25.9 Hz), 43.75; MS (APCI+) 294 (M+1, 100); IR (KBr) 1673,  
 1592, 1228  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{14}\text{H}_{12}\text{FNO}_3\text{S}$  C, 57.33/57.48; H,  
 5 4.12/4.27; N, 4.78/4.67.

### EXAMPLE 3B

#### 4-Fluoro-2-(4-methanesulfonyl-phenylamino)-benzoic acid (3).

A solution of **1** (Scheme 1B) (0.4458 g, 0.00152 mole) and tetrabutyl-  
 10 ammonium oxon (1.1 g, 0.0030 mole) in  $\text{CH}_2\text{Cl}_2$  (20 ml) was stirred at room  
 temperature for 16 hours. TLC showed the presence of starting material; so  
 additional 1.1 g (0.0030 mole) of the tetrabutylammonium oxon was added  
 and reaction mixture stirred for 16 more hours. The reaction mixture was  
 loaded on to a silica column and eluted with  $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$  (9.75:0.25) and  
 15 the fast moving fraction collected and concentrated to give **3** as a white solid.  
 Yield, 0.3856 g (82%); mp 200-202  $^\circ\text{C}$ ;  $^1\text{H}$ -NMR (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.78 (s,  
 1H), 8.13 (dd, 1H,  $J$ =8.9, 6.5 Hz), 7.94-7.38 (AB quartet, 4H), 7.10 (dd, 1H,  
 $J$ =11.3, 2.4 Hz), 6.66-6.61 (m, 1H), 3.09 (s, 3H);  $^{13}\text{C}$ -NMR (100 MHz;  $\text{CDCl}_3$ )  
 $\delta$  171.52, 167.28 (d,  $J_{C-F}$ =254.9 Hz), 148.32, 145.21, 135.59 (d,  $J_{C-F}$ =11.5 Hz),  
 20 134.50, 129.39, 120.62, 108.74, 107.46 (d,  $J_{C-F}$ =22.8 Hz), 101.61 (d,  $J_{C-}$   
 $F$ =26.7 Hz), 44.78;  $^{19}\text{F}$ -NMR (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -100.29 to -100.45 (m); MS  
 (APCI+) 310 (M+1, 100); (APCI-) 308 (M-1, 100); Anal. calcd/found for:  
 $\text{C}_{14}\text{H}_{12}\text{FNO}_4\text{S} \cdot 0.75 \text{H}_2\text{O}$  C, 52.08/52.36; H, 4.22/3.88; N, 4.34/4.26.

25

### EXAMPLE 4B

#### 2-methyl-4-trimethylsilylanylethynyl-aniline (5)

To a solution of 4-iodo-2-methyl-aniline (2.33g, 10 mmol),  
 bis(triphenylphosphine)palladium(II)chloride (1.4g, 0.2 mmol), CuI (0.19 g, 0.1  
 30 mmol) in  $\text{Et}_3\text{N}$  (40 ml) at ice-bath temperature, (trimethylsilyl)acetylene (1.18  
 g, 12 mmol) was added dropwise (Scheme 2B). After an hour stirring, the ice-  
 bath was removed and the reaction mixture heated at 40 $^\circ\text{C}$  (oil-bath  
 temperature) for one hour; cooled to room temperature and the solvent

removed. The residue was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O. The Et<sub>2</sub>O layer was separated, dried (MgSO<sub>4</sub>) and concentrated to give an oil. The oil was purified by silica column, eluting with CH<sub>2</sub>Cl<sub>2</sub>. The fraction with R<sub>f</sub> = 0.37 was collected and concentrated to give 2-methyl-4-trimethylsilanylethynylaniline as a dark brown oil.  
Yield 1.50 g (83%).

#### EXAMPLE 5B

##### 4-Fluoro-2-(2-methyl-4-trimethylsilanylethynyl-phenylamino)-benzoic acid (6)

Continuing after Example 4B, to a solution of 2-methyl-4-trimethylsilanylethynylaniline (1.50 g, 0.008 mole) in THF (10 ml) at -78°C, LDA (2 M in THF, 6 ml, 0.012 mole) was added and the mixture was stirred at -78°C for 30 minutes. Solid 2,4-difluoro-benzoic acid (0.633 g, 0.004 mole) was added and the stirred for 16 hours while it warmed up to room temperature. The solvents were removed and water (30 ml) and Et<sub>2</sub>O (50 ml) added to the oil residue. The mixture was stirred vigorously and the Et<sub>2</sub>O layer separated, dried (MgSO<sub>4</sub>) and concentrated to give a brown solid. The solid was purified on silica column, eluted with CH<sub>2</sub>Cl<sub>2</sub>. The fraction with R<sub>f</sub> = 0.37 was collected and concentrated to give a light brown solid. The solid was added to pentane; some insoluble brown particulate was separated by filtration and discarded. The pentane layer was concentrated to give **6** as a light yellow solid. Yield 0.65 g (47%); mp 170-171°C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 9.33 (s, 1H), 8.05 (dd, 1H, J=8.9, 6.8 Hz), 7.43 (d, 1H, J=1.2 Hz), 7.35 (dd, 1H, J=8.2, 1.7 Hz), 7.25 (d, 1H, J=8.2 Hz), 6.53 (dd, 1H, J=11.8, 2.4 Hz), 6.47-6.42 (m, 1H), 2.25 (s, 3H), 0.26 (s, 9H); <sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>) δ 172.86, 167.61 (d, J<sub>C-F</sub>=253.3), 151.24 (d, J<sub>C-F</sub>=12.3 Hz), 138.28, 135.38 (d, J<sub>C-F</sub>=11.4 Hz), 134.85, 132.82, 130.63, 123.81, 119.91, 106.63, 105.23 (d, J<sub>C-F</sub>=22.8 Hz), 104.77, 99.98 (d, J<sub>C-F</sub>=26.7 Hz), 94.05, 17.78, 0.00; MS (APCI+) 342 (M+1, 100); IR (KBr) 2151, 1661, 1249 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>19</sub>H<sub>20</sub>FNO<sub>2</sub>Si C, 66.83/67.02; H, 5.90/6.00; N, 4.10/4.09; F, 5.56/5.45.

## EXAMPLE 6B

4-Fluoro-2-(2-methyl-4-ethynyl-phenylamino)-benzoic acid (7).

To a solution of **6** in CH<sub>3</sub>OH (30 ml), aqueous 1N KOH (10 ml) was added. After stirring at room temperature for 16 hours, the CH<sub>3</sub>OH was removed and the aqueous layer was acidified with 6N HCl (Scheme 2B). The resulting white precipitation was extracted in to Et<sub>2</sub>O, the Et<sub>2</sub>O layer was dried (MgSO<sub>4</sub>) and concentrated to give **7** as tan colored solid. Yield 0.4274 g (91%); mp 177-178 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 9.35 (s, 1H), 8.08-8.04 (m, 1H), 7.44 (s, 1H), 7.38-7.25 (m, 2H), 6.57 (d, 1H, J=11.8 Hz), 6.48-6.44 (m, 1H), 3.08 (s, 1H), 2.27 (s, 3H); <sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>) δ 172.84, 167.61 (d, J<sub>C-F</sub>=253.3), 151.15 (d, J<sub>C-F</sub>=12.3 Hz), 138.63, 135.40 (d, J<sub>C-F</sub>=12.3 Hz), 135.00, 132.87, 130.81, 123.76, 118.79, 106.75, 105.33 (d, J<sub>C-F</sub>=22.8 Hz), 100.03 (d, J<sub>C-F</sub>=26.0 Hz), 83.37, 17.83, 0.00; <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -101.24 to -101.31 (m); MS (APCI+) 270 (M+1, 100); IR (KBr) 3315, 1672, 1594, 1253 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>16</sub>H<sub>12</sub>FNO<sub>2</sub> C, 71.37/71.08; H, 4.49/4.82; N, 5.20/5.09.

## EXAMPLE 7B

1-(4-nitro-phenyl)-1H-pyrrole (9a)

To a gently refluxing mixture of 4-nitroaniline (6.906 g, 0.05 mole), and sodium acetate (23 g, 0.28 mole) in acetic acid (100 ml) was added 2,5-dimethoxytetrahydrofuran (7.26 g, 7.12 ml, 0.055 mole) dropwise (Scheme 3B). After refluxing for 3 hours, the reaction mixture was poured on to crushed ice (~250 ml), basified with 10 % sodium hydroxide (250 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried (K<sub>2</sub>CO<sub>3</sub>) to afford the product as a dark brown oil. Yield 9.40 g (100 %).

## EXAMPLE 8B

1-(4-nitro-phenyl)-1H-pyrazole (9b)

A mixture of pyrazole (6.808 g, 0.1 mole) tetrabutylammonium bromide (3.22 g, 0.01 mole) and KOH (11.22 g, 0.2 mole) were ground together and sonicated for 16 hours. To this 1-fluoro-4-nitrobenzene (15.521 g, 11.67 ml,

0.11 mole) was added and the mixture sonicated for 24 hours. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried (MgSO<sub>4</sub>) and concentrated to give dark brown solid. This was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> (R<sub>f</sub> = 0.44) gave the product as a light brown solid. Yield 8.80 g (47 %); mp 171-172 °C; Anal. calcd/found for: C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub> C, 57.14/56.52; H, 3.73/3.62; N, 22.21/21.95.

#### EXAMPLE 9B

##### 3,5-dimethyl-1-(4-nitro-phenyl)-1H-pyrazole (9c)

To a solution of 4-nitro-phenyl-hydrazine (15.3 g, 0.1 mole) and 2,4-pentanedione (10.01 g, 10.27 ml, 0.1 mole) in EtOH (200 ml) were added 5 drops of concentrated HCl. The mixture was refluxed for 15 minutes; and the solvent removed to give a gummy product. This was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> gave the desired product (R<sub>f</sub> = 0.10) as a brown solid. Yield 7.22 g (33 %).

#### EXAMPLE 10B

##### 4-Pyrrol-1-yl-phenylamine (10a)

Catalytic reduction (H<sub>2</sub>/RaNi (5 g) /THF) of 1-(4-nitro-phenyl)- 1H-pyrrole (9.69 g, 0.05149 mole) at 51 psi gave crude product as an oil (Scheme 3B). The product was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> (R<sub>f</sub> = 0.13) gave the pure product as white solid. Yield 8.06 g (99 %); mp 80-81 °C.

25

#### EXAMPLE 11B

In a manner similar to the preparation of 4-pyrrol-1-yl-phenylamine, the following were prepared:

4-1H-Pyrazol-1-yl-phenylamine (10b). Dark brown oil, yield 6.26 g (100 %).

Benzenamine, 4-(3,5-dimethyl-1H-pyrazol-1-yl) (10c). Dark brown oil.

Yield 6.45 g (100 %).

#### EXAMPLE 12B

##### 4-Fluoro-2-(4-pyrrol-1-yl-phenylamino)-benzoic acid (11a)

- 5 To a solution of 4-pyrrol-1-yl-phenylamine (3.16 g, 0.02 mole) in THF (30 ml) at  $-78^{\circ}\text{C}$ , a solution of LDA (2M, 15 ml, 0.03 mole) was added and the mixture stirred for 30 minutes. Solid 2,4-difluorobenzoic acid was added and the reaction mixture stirred for 16 hours as it warmed up to room temperature. The solvent was removed and ether (100 ml) added to the dark oily residue.
- 10 This was stirred vigorously and the insoluble gummy precipitate separated by filtration. The gummy residue was dissolved in  $\text{H}_2\text{O}$ , acidified to pH 1 with 10% HCl, and extracted with  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$  layer was dried ( $\text{MgSO}_4$ ) and concentrated to give the target compound as a brown solid. Yield 2.74 g (93 %); mp  $223-225^{\circ}\text{C}$  (DEC);  $^{19}\text{F}$ -NMR (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -101.44 (s); MS
- 15 (APCI+) 297 (M+1, 100); IR (KBr) 1658, 1526,  $1254\text{ cm}^{-1}$ .

In a manner similar to the preparation of 4-Fluoro-2-(4-pyrrol-1-yl-phenylamino)-benzoic acid, the following were prepared:

- 20 4-Fluoro-2-(4-pyrazol-1-yl-phenylamino)-benzoic acid (11b). Light brown solid, mp  $212-213^{\circ}\text{C}$ .

- 2-[4-(3,5-Dimethyl-pyrazol-1-yl)-phenylamino]-4-Fluoro benzoic acid (11c). Tan powder, mp  $198-200^{\circ}\text{C}$ .

25

## EXAMPLE 1C

5     Preparation of 2-(2-chloro-4-iodo-phenylamino)-5-dimethylsulfamoyl-3,4-difluoro-benzoic acid methyl ester (APK IC<sub>50</sub>=222 nM)

      Step a: Preparation of 1-dimethylsulfamoyl-2,3,4-trifluorobenzene

      To a gently stirring solution comprised of 2,3,4-trifluorobenzenesulfonyl chloride (5.70 g, 0.0247 mol) in 1,2-dichloroethane (200 ml) was introduced by  
10     bubbling gaseous anhydrous dimethylamine. The mixture became cloudy after several minutes and was subsequently washed with water (200 ml), 6 N aqueous hydrochloric acid (200 ml), brine (200 ml), was dried over anhydrous magnesium sulfate, and was concentrated *in vacuo* to obtain a yellow oil. The  
15     crude product was purified by flash chromatography. Elution with dichloromethane afforded 3.40 g of a white solid; 58 % yield; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 7.63-7.56 (m, 1H), 7.12-7.04 (m, 1H), 2.812 (s, 3H), 2.807 (s, 3H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -124.91 to -125.03 (m), -127.98 to -128.03 (m), -156.41 to -156.53.

20     Step b: Preparation of 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid

      To a cold (-78 °C) stirring solution comprised of 1-dimethylsulfamoyl-2,3,4-trifluorobenzene in anhydrous tetrahydrofuran (60 ml) under a nitrogen atmosphere was added a commercially available lithium diisopropylamide solution (Aldrich, 2.0 M in tetrahydrofuran/heptane/ethylbenzene, 7.5 ml,  
25     0.0150 mol). After stirring for about ten minutes, the purple solution was transferred via canula to a cold, stirring, saturated carbon dioxide in diethyl ether solution (200 ml). The reaction mixture took on a dull burgundy color. The cold bath was removed and the reaction mixture warmed to ambient temperature over one hour. The mixture was then carefully quenched with  
30     10 % aqueous hydrochloric acid (200 ml). The layers were separated. The organic phase was extracted twice (200, 100 ml portions) with 10 % (wt.) aqueous sodium hydroxide. The combined aqueous alkaline extracts were treated with concentrated aqueous hydrochloric acid (100 ml) to pH 0. A white precipitate formed. The suspension was allowed to cool, then was  
35     extracted with diethyl ether (600 ml). The organic extract was dried over

anhydrous magnesium sulfate and was concentrated *in vacuo* to afford 2.70 g of an off-white solid; 67.5 % yield; mp 225-228 °C; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 14.08 (broad s, 1H), 8.02-7.97 (m, 1H), 2.75 (s, 3H), 2.74 (s, 3H) <sup>19</sup>F-NMR (376 MHz; DMSO) δ -122.50 to -122.63 (m), -122.95 to -123.08 (m), -154.49 to -154.61 (m); MS (APCI+) 284 (M+1, 22), 238 (100); (APCI-) 282 (M-1, 85), 259 (94), 238 (46), 216 (91), 195 (100); IR (KBr) 1702 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>9</sub>H<sub>8</sub>F<sub>3</sub>NO<sub>4</sub>S C, 38.17/38.40; H, 2.85/2.90; N, 4.95/4.80; F, 20.12/19.75; S, 11.32/11.12.

10 Step c: Preparation of 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid methyl ester

The solid 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid (1.47 g, 0.00519 mol) and *p*-toluenesulfonic acid catalyst (17.1 mg) were dissolved in methanol (125 ml). The stirring mixture was brought to reflux under a nitrogen atmosphere for 51 hours. The reaction mixture was concentrated *in vacuo* to give a solid. The product was partitioned between diethyl ether (200 ml) and saturated aqueous potassium carbonate (75 ml). The layers were separated and the organic phase was washed with water (75 ml), brine (75 ml), was dried over anhydrous potassium carbonate, and was concentrated *in vacuo* to afford 0.15 g of an off-white solid; 10 % yield; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 8.23-8.19 (m, 1H), 3.92 (s, 3H), 2.83 (s, 6H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -120.79 to -121.02 (m), -153.69 to -153.80.

25 Step d: Preparation of 2-(2-chloro-4-iodo-phenylamino)-5-dimethylsulfamoyl-3,4-difluoro-benzoic acid methyl ester

To a stirring cold (-78 °C) solution comprised of 2-chloro-4-iodoaniline (0.143 g, 5.64x10<sup>-4</sup> mol) in anhydrous tetrahydrofuran (5 ml) under a nitrogen atmosphere was added a commercially available lithium diisopropylamide solution (Aldrich, 2.0 M in tetrahydrofuran/heptane/ethylbenzene, 0.300 ml, 6.0x10<sup>-4</sup> mol). After stirring for 5 minutes, a solution comprised of 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid methyl ester (0.15 g, 5.0x10<sup>-4</sup> mol) in tetrahydrofuran (10 ml) was added via syringe. The cold bath was removed and the reaction mixture was stirred for 2 hours. The reaction mixture was then partitioned between diethyl ether (125 ml) and saturated

aqueous sodium bicarbonate (125 ml). The aqueous bicarbonate phase was extracted with an additional portion (125 ml) of diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The oil was crystallized from heptane-ethyl acetate to afford 0.060 g of an off-white powder; 23 % yield; mp 154-156 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 9.74 (s, 1H), 8.30 (d, 1H, J=7.1 Hz), 7.72 (s, 1H), 7.49 (d, 1H, J=8.3 Hz), 6.73-6.69 (m, 1H), 3.92 (s, 3H), 2.84 (s, 3H), 2.83 (s, 3H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -123.90 (d), -139.55 (d).

## EXAMPLE 2C

Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-benzamide (PD 219622)

### Step a: Preparation of 1-bis-(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzene

To a stirring solution comprised of *bis*-4-methoxybenzylamine (2.5 g, 9.7x10<sup>-3</sup> mol) and diisopropylethylamine (1.7 ml, 9.7x10<sup>-3</sup> mol) in dichloromethane (50 ml) at 0 °C under nitrogen atmosphere was added liquid 2,3,4-trifluorobenzenesulfonyl chloride (2.26 g, 9.5x10<sup>-3</sup> mol) directly. The mixture was stirred cold for ten minutes. The ice-water bath was removed and the mixture was stirred for an additional 15 minutes and was then diluted with dichloromethane to 350 ml volume and was washed with saturated aqueous ammonium chloride (200 ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford 4.99 g of a sticky white solid. The crude product was recrystallized from hexanes-acetone to afford 3.00 g of white needles; 70 % yield; mp 87-90 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 7.64-7.58 (m, 1H), 7.04-6.99 (m, 1H), [6.97 (d, 4H, J=8.5 Hz), 6.75 (d, 4H, J=8.8 Hz) AB q], 4.33 (s, 4H), 3.76 (s, 6H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -125.44 to -125.56 (m), -128.61 to -128.72 (m), -156.91 to -157.03 (m); MS (APCI+) 121 (M-330, 100); (APCI-) 330 (M-121, 18), 195 (M-256, 100); IR (KBr) 1612, 1517, 1506, 1465, 1258, 1240, 1156, 1037, 1030 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>22</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>4</sub>S C, 58.53/57.98; H, 4.47/4.61; N, 3.10/2.85.



Step b: Preparation of 5-bis-(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoic acid

To a stirring solution comprised of 1-bis-(4-methoxybenzyl)sulfamoyl-  
5 2,3,4-trifluorobenzene (2.95 g,  $6.5 \times 10^{-3}$  mol) in tetrahydrofuran (60 ml) at  $-78$  °C was added a solution comprised of 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich, 3.35 ml,  $6.7 \times 10^{-3}$  mol). After several minutes of stirring, the dark solution was transferred via canula over five minutes to a stirring solution comprised of carbon dioxide (excess) in  
10 diethyl ether at  $-78$  °C. A white precipitate immediately formed. The cold bath was removed and the reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was quenched with 200 ml of dilute aqueous hydrochloric acid. The layers were separated and the organic phase was dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give 2.82 g of an off-  
15 white solid. Recrystallization from dichloromethane (150 ml) afforded 2.10g of the white powder product; 65 % yield; mp  $158-161$  °C;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  7.80-7.76 (m, 1H), 7.05-6.74 (AB q, 8H,  $J=8.6$  Hz), 4.33 (s, 4H), 3.66 (s, 6H);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$   $-123.28$  to  $-123.36$  (m),  $-124.12$  to  $-124.21$  (m),  $-155.41$  to  $-155.53$  (m); MS (APCI-) 494 (M-1, 47), 216 (89),  
20 195 (100); IR (KBr) 3420, 2954, 2838, 1695, 1613, 1512, 1347, 1238, 1152, 1079  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{23}\text{H}_{20}\text{F}_3\text{NO}_6\text{S}$  C, 55.76/55.85; H, 4.07/4.02; N, 2.83/2.71; F, 11.50/11.41; S, 6.47/6.25.

25 Step c: Preparation of 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (PD 215729)

To a stirring solution comprised of 2-chloro-4-iodoaniline (0.53 g,  $2.0 \times 10^{-3}$  mol) in tetrahydrofuran (10 ml) at  $-78$  °C under a nitrogen atmosphere was added a solution comprised of 1.0 M lithium bis(trimethylsilyl)amide in tetrahydrofuran (Aldrich, 4.1 ml,  $4.1 \times 10^{-3}$  mol).  
30 Within several minutes the solution became a thick light-green suspension. To this mixture was added a solution comprised of lithium 5-bis-(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoate in tetrahydrofuran, which was prepared by adding 2.0 ml of the Aldrich lithium bis(trimethylsilyl)amide solution (0.0020 mmol) to a solution comprised of 5-bis-(4-

methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoic acid (1.00 g,  $2.0 \times 10^{-3}$  mol) in tetrahydrofuran (10 ml) at  $-78^\circ\text{C}$ . The reaction mixture was stirred for 15 minutes and was then concentrated *in vacuo* to a crude semisolid. The semisolid was taken up into diethyl ether (250 ml) and was washed with 1 % aqueous hydrochloric acid (150 ml). The ether phase was then washed with neutral water (200 ml, pH 4 after wash), a second portion of water (200 ml, pH 6 after wash), and brine (200 ml). The organic phase was then dried ( $\text{MgSO}_4$ ) and was concentrated *in vacuo* to give 1.88 g of a sticky residue which was crystallized from toluene-heptane to afford 1.12 g of an off-white powder; 76 % yield; mp  $162-166^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  9.86 (s, 1H), 7.92 (d, 1H,  $J=6.8$  Hz), 7.86 (d, 1H,  $J=1.7$  Hz), 7.60 (dd, 1H,  $J=8.5, 1.7$  Hz), 7.06-7.04/6.78-6.75 (AB q, 8H,  $J=8.5$  Hz), 6.93-6.89 (m, 1H), 4.31 (s, 4H), 3.66 (s, 6H);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$   $-127.22$  (d),  $-141.36$  (d); MS (APCI+) 729 (M+1, 1), 256 (50), 121 (100); (APCI-) 727 (M-1, 100); IR (KBr) 1698, 1673, 1513,  $1251\text{ cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{29}\text{H}_{24}\text{ClF}_2\text{IN}_2\text{O}_6\text{S}$  C, 47.78/47.93; H, 3.32/3.33; N, 3.84/3.80; Cl, 4.86/4.84; F, 5.21/5.46; I, 17.41/17.16; S, 4.40/4.29.

Step d: Preparation of 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD 218774)

To a stirring solution comprised of 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (0.935 g,  $1.28 \times 10^{-3}$  mol), cyclopropylmethoxylamine hydrochloride (0.175 g,  $1.42 \times 10^{-3}$  mol), and diisopropylethylamine (0.75 ml,  $4.26 \times 10^{-3}$  mol) in a 1:1 v/v tetrahydrofuran-dichloromethane mixture (50 ml) was added solid PyBOP ([benzotriazolyloxy]tripyrrolidino phosphonium hexafluorophosphate, Advanced ChemTech, 0.76 g,  $1.46 \times 10^{-3}$  mol). The reaction mixture was stirred for one hour, was then evaporated to a crude residue which was purified by flash silica column chromatography. Elution with a gradient (25 % dichloromethane to 75 % dichloromethane in hexanes) afforded 0.63 g of the off-white powder product; 62 % yield; mp  $70 \rightarrow 300^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  11.92 (s, 1H), 9.35 (s, 1H), 7.60 (s, 1H), 7.50-7.45 (m, 1H), 7.34 (d, 1H,  $J=8.5$  Hz), 6.82-6.54 (AB q, 8H,  $J=8.3$  Hz), 6.59-6.54 (m, 1H), 4.09 (s,

4H), 3.46 (s, 6H), 0.90-0.80 (m, 1H), 0.30-0.25 (m, 2H), 0.03-0.00 (m, 2H);  
<sup>19</sup>F-NMR (376 MHz; DMSO) δ -129.05 (s), -140.23 (d, J=18.3 Hz); MS  
(APCI+) 798 (M+1, 70); (APCI-) 796 (M-1, 15), 726 (50), 131 (100); IR (KBr)  
1642, 1611, 1584, 1513, 1478 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>33</sub>H<sub>31</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>6</sub>S  
5 C, 49.67/49.88; H, 3.92/3.95; N, 5.27/5.19.

Step e: Preparation of 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-benzamide (PD 219622)

A reaction solution comprised of 5-bis-(4-methoxybenzyl)sulfamoyl-2-  
10 (2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide  
(0.1010 g, 1.266x10<sup>-4</sup> mol) in trifluoroacetic acid (4 ml) was stirred at ambient  
temperature for 24 hours. The mixture was vacuum filtered and the  
precipitate rinsed with hexanes to afford 28.6 mg of a pale lavender powder;  
42 % yield; mp 219-227 °C DEC; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 11.89 (s, 1H),  
15 9.08 (s, 1H), 7.60 (s, 3H), 7.55 (d, 1H, J=6.9 Hz), 7.32 (d, 1H, J=8.6 Hz), 6.63-  
6.59 (m, 1H), 3.40 (d, 2H, J=6.6 Hz), 0.90-0.80 (m, 1H), 0.30-0.26 (m, 2H),  
0.05-0.00 (m, 2H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ  
-130.61 (s), -140.38 (d, J=21.4 Hz); MS (APCI+) 558 (M+1, 70), 282 (100);  
(APCI-) 556 (M-1, 73), 486 (100); IR (KBr) 3390, 3283, 1652, 1513, 1477,  
20 1163 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>17</sub>H<sub>15</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>4</sub>S · 0.1 C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub> C,  
36.30/36.31; H, 2.67/2.55; N, 7.38/7.00.

EXAMPLE 3C

25 Preparation of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-5-sulfamoyl-benzamide (PD 224213)

To a stirring solution comprised of 5-bis-(4-methoxybenzyl)sulfamoyl-2-  
(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (0.67 g, 9.2x10<sup>-4</sup> mol),  
O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.113 g, 9.65x10<sup>-4</sup> mol), and  
30 diisopropylethylamine (0.50 ml, 2.9x10<sup>-3</sup> mol) in a 1:1 v/v tetrahydrofuran-  
dichloromethane mixture (20 ml) was added solid PyBOP  
([benzotriazolyloxy]tripyrrolidino phosphonium hexafluorophosphate,  
Advanced ChemTech, 0.52 g, 1.0x10<sup>-3</sup> mol). The reaction mixture was stirred  
for 30 minutes, was concentrated *in vacuo* to a yellow oil, and was crystallized  
35 from methanol to afford 0.35 g of the off-white amorphous intermediate; 46 %

yield; the intermediate was dissolved in trifluoroacetic acid (10 ml) and was stirred at ambient temperature for 16 hours. The mixture was vacuum filtered to collect the precipitate, which was recrystallized from methanol-chloroform to afford 0.055 g of the tan powder product; 26 % yield from intermediate; mp 230-236 °C DEC; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 11.73 (s, 1H), 9.46 (s, 1H), 9.38 (s, 1H), 7.80-7.75 (m, 2H), 7.79 (s, 2H), 7.50 (d, 1H, J=8.5 Hz), 6.82-6.78 (m, 1H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -130.83 (s), -139.24 (s); MS (APCI+) 504 (M+1, 53), 488 (90), 471 (100); (APCI-) 502 (M-1, 12), 486 (100); IR (KBr) 3295, 1652, 1636, 1519, 1477, 1315, 1157 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>13</sub>H<sub>9</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>4</sub>S · 0.41 CHCl<sub>3</sub> C, 29.15/29.05; H, 1.72/1.66; N, 7.60/7.21.

#### EXAMPLE 4C

Preparation of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-sulfamoyl-benzoic acid (PD 215730)  
Solid 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (0.0995 g, 1.36x10<sup>-4</sup> mol) was dissolved in trifluoroacetic acid (5 ml) under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 65 hours. The mixture was vacuum filtered to isolate 55.2 mg of a fine white precipitate. The crude product was recrystallized from chloroform to afford 31.8 mg of the fluffy white solid product; 48 % yield; mp 295-296 °C DEC; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 9.77 (s, 1H), 8.16 (d, 1H, J=7.3 Hz), 7.82 (s, 3H), 7.56 (d, 1H, J=8.5 Hz), 6.97-6.92 (m, 1H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -128.47 (s), -141.13 (d, 19.8 Hz); MS (APCI+) 489 (M+1, 5), 102 (100); (APCI-) 491 (32), 490 (18), 489 (100), 488 (18), 487 (M-1, 75); IR (KBr) 3372, 3244, 1688 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>13</sub>H<sub>8</sub>ClF<sub>2</sub>IN<sub>2</sub>O<sub>4</sub>S C, 31.96/32.19; H, 1.65/1.81; N, 5.73/5.37.

#### EXAMPLE 5C

Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-benzamide (PD 250253)

Step a: Preparation of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-dimethylsulfamoyl-benzoic acid (PD 224339)

To a stirring solution comprised of 5-dimethylsulfamoyl-2,3,4-trifluorobenzoic acid (1.00 g,  $3.53 \times 10^{-3}$  mol) in tetrahydrofuran (15 ml) at  $-78$  °C under a nitrogen atmosphere was added a 1.0 M solution of lithium *bis*(trimethylsilyl)amide in tetrahydrofuran (Aldrich, 3.6 ml,  $3.6 \times 10^{-3}$  mol). A lithium 2-chloro-4-iodoanilide suspension formed by adding a 1.0 M solution of lithium *bis*(trimethylsilyl)amide solution (7.2 ml,  $7.2 \times 10^{-3}$  mol) to a solution comprised of 2-chloro-4-iodoaniline (0.94 g,  $3.63 \times 10^{-3}$  mol) in tetrahydrofuran (15 ml) at  $-78$  °C was added via canula to the lithium 5-dimethylsulfamoyl-2,3,4-trifluorobenzoate suspension. The cold bath was removed and the reaction mixture was stirred for one hour. The mixture was concentrated *in vacuo* to a crude solid. The crude product was suspended in diethyl ether (200 ml), to which suspension hydrogen chloride gas was introduced to produce a white precipitate. The precipitate was removed by vacuum filtration. The filtrate was concentrated *in vacuo* to give a dull-colored solid, which was triturated with hexanes-dichloromethane to afford 1.31 g of the white powder product; 72 % yield; mp 218-222 °C;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  9.89 (s, 1H), 8.06 (d, 1H,  $J=6.1$  Hz), 7.85 (d, 1H,  $J=1.9$  Hz), 7.58 (dd, 1H,  $J=8.5, 1.9$  Hz), 7.03 (dd, 1H,  $J=8.3, 6.6$  Hz), 2.71 (s, 6H);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$  -125.58 (d,  $J=18.3$  Hz), -140.14 (d,  $J=16.8$  Hz); MS (APCI+) 519 (40), 518 (15), 517 (M+1, 100); (APCI-) 517 (6), 516 (2), 515 (M-1, 5), 480 (45), 127 (100); IR (KBr) 3346, 1665, 1487, 1283  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{15}\text{H}_{12}\text{ClF}_2\text{IN}_2\text{O}_4\text{S}$  C, 34.87/34.98; H, 2.34/2.32; N, 5.42/5.32.

25 Step b: Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-benzamide

To a suspension comprised of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-dimethylsulfamoyl-benzoic acid (0.5 g,  $9.68 \times 10^{-4}$  mol) and cyclopropylmethoxylamine hydrochloride (0.13 g,  $1.05 \times 10^{-3}$  mol) in a 1:1 v/v mixture of dichloromethane-tetrahydrofuran (10 ml) was added diisopropylethylamine (0.65 ml,  $3.73 \times 10^{-3}$  mol) followed by the addition of solid PyBOP (0.55 g,  $1.06 \times 10^{-3}$  mol). The reaction mixture was stirred at ambient temperature for three days. The mixture was concentrated *in vacuo* to a red oil. The crude product was treated with 10 % aqueous hydrochloric acid (150

ml) and was extracted with diethyl ether (150 ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to a crude solid. The solid was triturated with dichloromethane-hexanes and recovered by vacuum filtration to afford 0.3558 g of the white powder product; 63 % yield; mp 222-225 °C DEC;

5 <sup>1</sup>H-NMR (400 MHz; DMSO) δ 11.97 (s, 1H), 9.32 (s, 1H), 7.60 (d, 1H, J=1.9 Hz), 7.49 (d, 1H, J=5.8 Hz), 7.33 (dd, 1H, J=8.4, 1.9 Hz), 6.70 (dd, 1H, 8.4, 6.3 Hz), 3.43 (d, 2H, J=7.2 Hz), 2.53 (s, 6H), 0.87-0.83 (m, 1H), 0.30-0.25 (m, 2H), 0.03-0.00 (m, 2H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -127.67 (d, J=19.8 Hz), -139.32 (d, J=19.8 Hz); MS (APCI+) 586 (M+1, 100); (APCI-) 584 (M-1, 40),

10 514 (100); IR (KBr) 3263, 1644, 1585, 1507, 1480 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>19</sub>H<sub>19</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>4</sub>S C, 38.96/39.08; H, 3.27/3.18; N, 7.17/7.17.

## EXAMPLE 6C

15 Preparation of N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methyl-phenylamino)-benzamide (PD 252745)

Step a: Preparation of 3,4-difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (PD 224340)

20 Same procedure and same scale as Example 4C, Step a, except 4-iodo-2-methylaniline was used instead of 2-chloro-4-iodoaniline; afforded 0.9592 g of the off-white powder product; 55 % yield; mp 235-238 °C; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 9.69 (s, 1H), 8.04 (d, 1H, J=6.1 Hz), 7.60 (d, 1H, J=1.5 Hz), 7.45 (dd, 1H, J=8.3, 1.7 Hz), 6.88 (dd, 1H, J=8.3, 5.4 Hz), 2.70 (s, 6H),

25 2.21 (s, 3H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -126.25 (d, J=16.8 Hz), -142.74 (d, J=19.8 Hz); MS (APCI+) 497 (M+1, 69), 357 (70), 316 (100); (APCI-) 495 (M-1, 3), 127 (100); IR (KBr) 3240, 1686, 1512, 1473, 1341, 1151 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>16</sub>H<sub>15</sub>F<sub>2</sub>IN<sub>2</sub>O<sub>4</sub>S C, 38.72/38.70; H, 3.05/3.01; N, 5.64/5.49.

30 Step b: Preparation of N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

Same procedure and same scale as Example 4C, Step b, except the product was purified by recrystallization from absolute ethanol to afford 0.1718 g of the pale yellow microcrystalline product; 28 % yield; mp 171-172 °C; <sup>1</sup>H-

35 NMR (400 MHz; DMSO) δ 11.79 (s, 1H), 8.91 (s, 1H), 7.40 (d, 1H, J=4.3 Hz),

7.36 (s, 1H), 7.21 (d, 1H, J=8.2 Hz), 6.54 (dd, 1H, 8.2, 4.3 Hz), 3.30 (d, 2H, J=6.5 Hz), 2.52 (s, 6H), 2.00 (s, 3H), 0.85-0.75 (m, 1H), 0.29 (d, 2H, J=7.7 Hz), 0.01 (d, 2H, J=4.1 Hz); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -128.94 (s), -143.32 (d, J=19.8 Hz); MS (APCI+) 566 (M+1, 100); (APCI-) 564 (M-1, 85), 494 (100); IR (KBr) 1649, 1609, 1588, 1512, 1475 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>20</sub>H<sub>22</sub>F<sub>2</sub>IN<sub>3</sub>O<sub>4</sub>S C, 42.49/42.42; H, 3.92/3.78; N, 7.43/7.40.

#### EXAMPLE 7C

##### 10 Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-dimethylsulfamoyl-benzamide

###### Step a: Preparation of 4-methyl-benzene-N,N-dimethylsulfonamide

To a stirring solution comprised of *para*-toluenesulfonyl chloride in  
15 dichloromethane at 0 °C is introduced excess gaseous dimethylamine. The precipitate is removed by filtration and the filtrate is concentrated *in vacuo* to obtain the product.

###### 20 Step b: Preparation of 4-methyl-3-nitro-benzene-N,N-dimethylsulfonamide

To a gently stirring solution comprised of 1 molar equivalent of fuming nitric acid in excess concentrated sulfuric acid is added 1 molar equivalent of 4-methyl-benzene-N,N-dimethylsulfonamide in increments. The mixture is stirred for one hour and then poured over chilled water. The mixture is extracted with a suitable solvent like diethyl ether or dichloromethane. The  
25 organic phase is dried over a suitable drying agent like magnesium sulfate and concentrated *in vacuo* to afford a crude product which may be purified by normal methods such as chromatography or crystallization from a solvent like chloroform or heptane.

###### 30 Step c: Preparation of 3-amino-4-methyl-benzene-N,N-dimethylsulfonamide

The compound 4-methyl-3-nitro-benzene-N,N-dimethylsulfonamide is dissolved in ethanol. A catalyst like Raney nickel is added and the mixture hydrogenated in a shaker. The catalyst is removed by filtration. The solvent is removed *in vacuo* to give a product which may be purified if necessary by

chromatography or crystallization from an appropriate solvent like chloroform or heptane-ethyl acetate.

Step d: Preparation of 3-fluoro-4-methyl-benzene-N,N-dimethylsulfonamide

The compound 3-amino-4-methyl-benzene-N,N-dimethylsulfonamide is diazotized with an alkyl nitrite like *tert*-butyl nitrite under anhydrous conditions in a non-reactive solvent like tetrahydrofuran or dichloromethane. The intermediate diazonium species is then treated with pyridinium fluoride to give the product, which may be purified by chromatography or crystallization.

Step e: Preparation of 4-dimethylsulfamoyl-2-fluoro-benzoic acid

A mixture comprised of 3-fluoro-4-methyl-benzene-N,N-dimethylsulfonamide and potassium permanganate (2.2 molar equivalents) in water is brought to reflux for four hours. The reaction mixture is filtered through celite. The filtrate is treated with activated carbon and refiltered through fresh celite. The second filtrate is acidified with concentrated hydrochloric acid to pH 0. The mixture is allowed to cool and is extracted with diethyl ether. The organic phase is dried over a drying agent like magnesium sulfate and is concentrated *in vacuo*. The product may be purified by recrystallization from an appropriate solvent like ethanol or chloroform.

Step f: Preparation of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-benzoic acid

To a stirring cold (-78 °C) solution comprised of 2-chloro-4-iodoaniline (1 molar equivalent) in anhydrous tetrahydrofuran under a nitrogen atmosphere is added a commercially available lithium diisopropylamide solution (Aldrich, 2.0 M in tetrahydrofuran/heptane/ethylbenzene, 1 molar equivalent). After stirring for 5 minutes, a solution comprised of 4-dimethylsulfamoyl-2-fluoro-benzoic acid (1 molar equivalent) in tetrahydrofuran is added. The cold bath is removed and the reaction mixture is stirred for 2 hours. The reaction mixture is then partitioned between diethyl ether and dilute aqueous hydrochloric acid. The organic phase is washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to afford



a product which may be purified by chromatography of recrystallization from an appropriate solvent like chloroform or heptane-ethanol.

5      Step g: Preparation of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-benzoic acid O-(tetrahydro-2H-pyran-2-yl)-oxyamide

          A solution comprised of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-benzoic acid, O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (1.25 molar equivalents), benzotriazole-1-yl-oxy-*tris*-pyrrolidino-phosphonium  
10      hexafluorophosphate (1.25 molar equivalents), and diisopropylethylamine (3 molar equivalents) in 1:1 v/v tetrahydrofuran-dichloromethane is stirred for 30 minutes. The reaction mixture is concentrated *in vacuo* and the residue is purified by flash chromatography; elution with dichloromethane affords the desired product. The product may be recrystallized with an appropriate  
15      solvent like methanol if further purification is necessary.

Step h: Preparation of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-N-hydroxy-benzamide

          The compound 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-  
20      benzoic acid O-(tetrahydro-2H-pyran-2-yl)-oxyamide is dissolved in an appropriate hydrogen chloride-saturated solvent like methanol or ethanol. Once homogeneous, the solution is concentrated *in vacuo* to give the desired product. The product may be triturated with an appropriate solvent like chloroform or dichloromethane if further purification is necessary.

25

## D. Uses

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions relating to chronic pain, including neuropathic pain, as provided in the Summary section, as well as diseases or conditions modulated by the MEK cascade. For example, in one embodiment, the disclosed method relates to postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, crush injury, constriction injury, tissue injury, post-surgical pain, arthritis pain, or limb amputation

For example, local injuries can be treated with local or topical administration. Chronic pain affecting the entire body, such as diabetic neuropathy can be treated with systemic administration (injection or orally) of a disclosed composition. Treatment for chronic pain (e.g., post-operative pain) confined to the lower body can be administered centrally, e.g., epidurally. Formulations and methods of administration can include the use of more than one MEK inhibitor, or a combination of a MEK inhibitor and another pharmaceutical agent, such as an anti-inflammatory, analgesic, muscle relaxing, or anti-infective agent. Preferred routes of administration are oral, intrathecal or epidural, subcutaneous, intravenous, intramuscular, and, for non-human mammals, intraplantar, and are preferably epidural.

### 1. Dosages

Those skilled in the art will be able to determine, according to known methods, the appropriate dosage for a patient, taking into account factors such as age, weight, general health, the type of pain requiring treatment, and the presence of other medications. In general, an effective amount will be between 0.1 and 1000 mg/kg per day, preferably between 1 and 300 mg/kg body weight, and daily dosages will be between 10 and 5000 mg for an adult subject of normal weight. Commercially available capsules or other

formulations (such as liquids and film-coated tablets) of 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

## 2. Formulations

Dosage unit forms include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses. Dosage unit forms can also be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants. Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption accelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.

Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.

## 3. Related compounds

The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as

salts, esters, amides, hydrates or solvated forms thereof; masked or protected forms; and racemic mixtures, or enantiomerically or optically pure forms.

Pharmaceutically acceptable salts, esters, and amides include carboxylate salts (e.g., C<sub>1-8</sub> alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic), amino acid addition salts, esters, and amides which are within a reasonable benefit/risk ratio, pharmacologically effective, and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium, quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C<sub>1-6</sub> alkyl amines and secondary di (C<sub>1-6</sub> alkyl) amines. Secondary amines include 5- or 6-membered heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C<sub>1-3</sub> alkyl primary amines, and di (C<sub>1-2</sub> alkyl)amines. Representative pharmaceutically acceptable esters of the invention include C<sub>1-7</sub> alkyl, C<sub>5-7</sub> cycloalkyl, phenyl, and phenyl(C<sub>1-6</sub>)alkyl esters. Preferred esters include methyl esters.

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. Some of these masked or protected compounds are pharmaceutically acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

## HYDROXYL PROTECTING GROUPS

Hydroxyl protecting groups include: ethers, esters, and protection for 1,2- and 1,3-diols. The ether protecting groups include: methyl, substituted methyl  
 5 ethers, substituted ethyl ethers, substituted benzyl ethers, silyl ethers and conversion of silyl ethers to other functional groups.

### Substituted Methyl Ethers

Substituted methyl ethers include: methoxymethyl, methylthiomethyl, *t*-  
 utylthiomethyl, (phenyldimethylsilyl) methoxymethyl, benzyloxymethyl, *p*-  
 10 ethoxybenzyloxymethyl, (4-methoxyphenoxy) methyl, guaiacolmethyl, *t*-  
 butoxymethyl, 4-pentenylloxymethyl, siloxymethyl, 2-methoxyethoxymethyl,  
 2,2,2-trichloroethoxymethyl, bis(2-chloro- ethoxy)methyl, 2-  
 (trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydro-pyranyl,  
 tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-  
 15 methoxytetrahydrothio-pyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxido,  
 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl,  
 tetrahydrofuranyl, tetrahydrothiofuranyl, and 2,3,3a,4,5,6,7,7a-octahydro-  
 7,8,8-trimethyl-4,7-ethanobenzofuran-2-yl.

### Substituted Ethyl Ethers

20 Substituted ethyl ethers include: 1-ethoxyethyl, 1-(2, chloroethoxy)ethyl,  
 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-  
 fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 2-(phenylselenyl)ethyl, *t*-  
 butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

### Substituted Benzyl Ethers

25 Substituted benzyl ethers include: *p*-methoxybenzyl, 3,4-dimethoxybenzyl,  
*o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl,  
*p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl,  
*p*, *p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl,  $\alpha$ -naphthyldiphenyl-  
 methyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl,  
 30 tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl,  
 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-  
 tris(levulinoyloxyphenyl) methyl, 4,4',4''tris(benzoyloxyphenyl)methyl, 3-

(imidazol-1-ylmethyl)bis(4',4''-dimethoxyphenyl)-methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl) xanthenyl, 9-(9-phenyl-10-oxo) anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl S,S-dioxido.

5        Silyl Ethers

Silyl ethers include: trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxyphenylsilyl.

10

ESTERS

Esters protecting groups include: esters, carbonates, assisted cleavage, miscellaneous esters, and sulfonates.

Esters

- 15        Examples of protective esters include: formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio) pentanoate, pivaloate, 20        adamantate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, and 2,4,6-trimethylbenzoate (mesitoate).

Carbonates

- Carbonates include: methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl) ethyl, 2-(phenylsulfonyl) ethyl, 2-(triphenylphosphonio) ethyl, 25        isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

Assisted Cleavage

- Examples of assisted cleavage protecting groups include: 2-iodobenzoate, 4-30        azido-butyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl) benzoate, 2-formylbenzene-sulfonate, 2-(methylthiomethoxy) ethyl carbonate, 4-

(methylthiomethoxymethyl) benzoate, and 2-(methylthiomethoxymethyl) benzoate.

#### Miscellaneous Esters

- 5 In addition to the above classes, miscellaneous esters include: 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl) phenoxyacetate, 2,4-bis(1,1-dimethylpropyl) phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenate (tigloate), *o*-(methoxycarbonyl) benzoate, *p*-P-benzoate,  $\alpha$ -
- 10 naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, *N*-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate.

#### Sulfonates

- Protective sulfates includes: sulfate, methanesulfonate(mesylate),
- 15 benzylsulfonate, and tosylate.

#### PROTECTION FOR 1,2- AND 1,3-DIOLS

The protection for 1,2 and 1,3-diols group includes: cyclic acetals and ketals, cyclic ortho esters, and silyl derivatives.

#### 20 Cyclic Acetals and Ketals

- Cyclic acetals and ketals include: methylene, ethylidene, 1-*t*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl) ethylidene, 2,2,2-trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-
- 25 dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

#### Cyclic Ortho Esters

- Cyclic ortho esters include: methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidene, 1,2-dimethoxyethylidene,  $\alpha$ -methoxybenzylidene, 1-(*N,N*-
- 30 dimethylamino)ethylidene derivative,  $\alpha$ -(*N,N*-dimethylamino) benzylidene derivative, and 2-oxacyclopentylidene.

## PROTECTION FOR THE CARBOXYL GROUP

### ESTERS

Ester protecting groups include: esters, substituted methyl esters, 2-  
5 substituted ethyl esters, substituted benzyl esters, silyl esters, activated  
esters, miscellaneous derivatives, and stannyl esters.

#### Substituted Methyl Esters

Substituted methyl esters include: 9-fluorenylmethyl, methoxymethyl,  
methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl,  
10 2-(trimethylsilyl)ethoxy-methyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl,  
 $\alpha$ -methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-  
phthalimidomethyl.

#### 2-Substituted Ethyl Esters

2-Substituted ethyl esters include: 2,2,2-trichloroethyl, 2-haloethyl, 1-  
15 chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl,  
2(*p*-nitrophenylsulfenyl)-ethyl, 2(*p*-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-  
(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl,  
cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl,  $\alpha$ -  
methylcinnamyl, phenyl, *p*-(methylmercapto)-phenyl, and benzyl.

#### 20 Substituted Benzyl Esters

Substituted benzyl esters include: triphenylmethyl, diphenylmethyl,  
bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-  
dibenzo-suberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-  
trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-  
25 methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl,  
piperonyl, and 4-P-benzyl.

#### Silyl Esters

Silyl esters include: trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-  
propyldimethylsilyl, phenyldimethylsilyl, and di- *t*-butylmethylsilyl.



Miscellaneous Derivatives

Miscellaneous derivatives includes: oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group, and pentaaminocobalt(III) complex.

5      Stannyl Esters

Examples of stannyl esters include: triethylstannyl and tri-*n*-butylstannyl.

## AMIDES AND HYDRAZIDES

Amides include: *N,N*-dimethyl, pyrrolidinyl, piperidinyl, 5,6-  
10 dihydrophenanthridinyl, *o*-nitroanilides, *N*-7-nitroindolyl, *N*-8-nitro-1,2,3,4-tetrahydroquinolyl, and *p*-P-benzenesulfonamides. Hydrazides include: *N*-phenyl, *N,N'*-diisopropyl and other dialkyl hydrazides.

PROTECTION FOR THE AMINO GROUP

15

CARBAMATES

Carbamates include: carbamates, substituted ethyl, assisted cleavage, photolytic cleavage, urea-type derivatives, and miscellaneous carbamates.

Carbamates

20 Carbamates include: methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydro-thioxanthyl)]methyl, and 4-methoxyphenacyl.

Substituted Ethyl

Substituted ethyl protective groups include: 2,2,2-trichloroethyl, 2-  
25 trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'-and 4'-pyridyl)ethyl, 2-(*N,N*-icyclohexylcarboxamido)- ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, connamyl, 4-nitrocinnamyl, quinolyl, *N*-  
30 hydroxypiperidinyl, alkylidithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, and diphenylmethyl.

Assisted Cleavage

Protection via assisted cleavage includes: 2-methylthioethyl,  
 2-methylsulfonyl ethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl,  
 5 4-methylthiophenyl, 2,4-dimethyl-thiophenyl, 2-phosphonioethyl,  
 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2cyanoethyl, *m*-chloro-*p*-  
 acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolyl-methyl, and  
 2-(trifluoromethyl)-6-chromonylmethyl.

Photolytic Cleavage

10 Photolytic cleavage methods use groups such as: *m*-nitrophenyl, 3,5-  
 dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-  
 nitrophenyl)methyl.

Urea-Type Derivatives

Examples of urea-type derivatives include: phenothiazinyl-(10)-carbonyl  
 15 derivative, *N*'-*p*-toluenesulfonylaminocarbonyl, and *N*'-  
 phenylaminothiocarbonyl.

Miscellaneous Carbamates

In addition to the above, miscellaneous carbamates include: *t*-amyl, *S*-benzyl  
 thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl,  
 20 cyclopropylmethyl, *p*-decyloxy-benzyl, diisopropylmethyl, 2,2-  
 dimethoxycarbonylvinyl, *o*-(*N,N*-dimethyl-carboxamido)-benzyl, 1,1-dimethyl-  
 3(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethyl-propynyl, di(2-pyridyl)methyl,  
 2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*(*p*'-  
 methoxyphenyl- azo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-  
 25 methyl-1-cyclopropyl- methyl, 1-methyl-(3,5-dimethoxyphenyl)ethyl, 1-methyl-  
 1(*p*-henylazophenyl)- ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-  
 pyridyl)ethyl, phenyl,  
*p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium) benzyl,  
 and 2,4,6-trimethylbenzyl.

30

AMIDESAmides

Amides includes: *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trichloroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridyl-carboxamide, *N*-benzoylphenylalanyl derivative, *N*-benzoyl, and *N*-*p*-phenylbenzoyl.

Assisted Cleavage

Assisted cleavage groups include: *N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N*'-dithiobenzoyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl) propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine derivative, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

Cyclic Imide Derivatives

Cyclic imide derivatives include: *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenyl-maleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

SPECIAL -NH PROTECTIVE GROUPS

Protective groups for –NH include: *N*-alkyl and *N*-aryl amines, imine derivatives, enamine derivatives, and *N*-hetero atom derivatives (such as *N*-metal, *N*-N, *N*-P, *N*-Si, and *N*-S), *N*-sulfenyl, and *N*-sulfonyl.

*N*-Alkyl and *N*-Aryl Amines

*N*-alkyl and *N*-aryl amines include: *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxyl]-methyl, *N*-3-acetoxypentyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl,

*N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and  
*N*-2-picolylamine *N*'-oxide.

#### Imine Derivatives

Imine derivatives include: *N*-1,1-dimethylthiomethylene, *N*-benzylidene,  
 5 *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene,  
*N*-[(2-pyridyl)mesityl]methylene,  
*N*-(*N*',*N*'-dimethylaminomethylene), *N*,*N*'-isopropylidene,  
*N*-*p*-nitrobenzylidene,  
*N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenyl-  
 10 methylene, and *N*-cyclohexylidene.

#### Enamine Derivative

An example of an enamine derivative is *N*-  
 (5,5-dimethyl-3-oxo-1-cyclohexenyl).

#### *N*-Hetero Atom Derivatives

15 *N*-metal derivatives include: *N*-borane derivatives, *N*-diphenylborinic acid  
 derivative, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, and  
*N*-copper or *N*-zinc chelate. Examples of *N*-*N* derivatives include: *N*-nitro,  
*N*-nitroso, and *N*-oxide. Examples of *N*-P derivatives include:  
*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl,  
 20 *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl.  
 Examples of *N*-sulfenyl derivatives include: *N*-benzenesulfenyl,  
*N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl,  
*N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxy-benzenesulfenyl, *N*-  
 triphenylmethylsulfenyl, and *N*-3-nitropyridinesulfenyl. *N*-sulfonyl derivatives  
 25 include: *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-  
 4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-  
 2,6-dimethyl-4-methoxy-benzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-  
 2,3,5,6-tetramethyl-4-methoxybenzene- sulfonyl, *N*-  
 4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-  
 30 2,6-dimethoxy- 4-methylbenzenesulfonyl, *N*-  
 2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl,

*N*- $\beta$ -trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)-benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl.

5 Disclosed compounds which are masked or protected may be prodrugs, compounds metabolized or otherwise transformed *in vivo* to yield a disclosed compound, e.g., transiently during metabolism. This transformation may be a hydrolysis or oxidation which results from contact with a bodily fluid such as blood, or the action of acids, or liver, gastrointestinal, or other enzymes.

10 Features of the invention are further described in the examples below.

## E. Examples

## BIOLOGICAL EXAMPLES

5

## Example 1

**Effect of PD 198306 on streptozocin-induced static allodynia**Animals

Male Sprague Dawley rats (250-300g), obtained from Bantin and Kingman, (Hull, U.K.) were housed in groups of 3. All animals were kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*. All experiments were carried out by an observer blind to drug treatments.

Development of diabetes in the rat

15 Diabetes was induced in rats by a single i.p. injection of streptozocin (50 mg/kg) as described previously (Courteix et al., 1993).

Evaluation of static allodynia

Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals right hind paw with von Frey hairs in ascending order of force ( 0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6 sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29 g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest amount of force required to elicit a response was recorded as the paw withdrawal threshold (PWT) in grams.

20  
25  
30

### Drugs

PD 198306 [N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide] and CI-1008 (pregabalin) were synthesized at Parke-Davis (Ann Arbor, MI, USA). PD 198306 was suspended in cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. Both compounds were administered orally. Streptozocin (Aldrich, UK) was dissolved in 0.9% w/v NaCl and administered intraperitoneally. Drug administrations were made in a volume of 1 ml/kg.

### Statistics

The static allodynia data were analysed using a Kruskal-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test.

### Experimental protocol

Static allodynia was assessed with von Frey hairs, before (baseline, BL) and 1h after oral administration of PD 198306 (30mg/kg, p.o.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (30mg/kg, p.o.) (test). Animals were administered again the same compounds on the following day, both in the morning and the afternoon. Static allodynia was assessed only before and 1h after the afternoon administration, in order to minimise the habituation of the animals to the testing conditions. Animals treated with pregabalin received water in the morning administration, in order to avoid the potential development of tolerance to the compound with repeated administration.

#### Day 1:

p.m.: BL

PD 198306

#### Day 2:

a.m.: PD 198306

Water

Vehicle

p.m.: BL

PD 198306

Pregabalin

Pregabalin

Vehicle

Vehicle

Test

Test

## 5 RESULTS

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (30mg/kg, p.o) had no effect on streptozocin-induced static allodynia 1h after administration (see below).

10 However, after the compound had been administered twice more on the following day, it significantly blocked streptozocin-induced static allodynia 1h after the third administration. The effects had disappeared by the following day (see FIG. 1).

15

### Example 2

## MATERIALS AND METHODS

### Animals

20 Male Sprague Dawley rats (250-300g), obtained from Charles River, Margate, U.K.) were housed in groups of 3-6. All animals were kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*. All experiments were carried out by an observer blind to drug treatments.

Diabetes was induced in rats by a single i.p. injection of streptozocin  
25 (50mg/kg) as described previously (Courteix et al., 1993).

### Development of Chronic Constriction Injury in the rat

Animals were anaesthetised with 2% isoflurane 1:4 O<sub>2</sub>/N<sub>2</sub>O mixture maintained during surgery via a nose cone. The sciatic nerve was ligated as  
30 previously described by Bennett and Xie, 1988. Animals were placed on a homeothermic blanket for the duration of the procedure. After surgical preparation the common sciatic nerve was exposed at the middle of the thigh



by blunt dissection through biceps femoris. Proximal to the sciatic trifurcation, about 7mm of nerve was freed of adhering tissue and 4 ligatures (4-0 silk) were tied loosely around it with about 1mm spacing. The incision was closed in layers and the wound treated with topical antibiotics.

5

#### Intrathecal injections

PD 198306 and pregabalin were administered intrathecally in a volume of 10  $\mu$ l using a 100  $\mu$ l Hamilton syringe by exposing the spine of the rats under brief isoflurane anaesthesia. Injections were made into the intrathecal space  
10 between lumbar region 5-6 with a 10 mm long 27 gauge needle. Penetrations were judged successful if there was a tail flick response. The wound was sealed with an autoclip and rats appeared fully awake within 2-3 min following injection.

#### Evaluation of static allodynia

15 Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals right  
20 hind paw with von Frey hairs in ascending order of force ( 0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest  
25 amount of force required to elicit a response was recorded as the paw withdrawal threshold (PWT) in grams.

#### Experimental protocol

Static allodynia was assessed with von Frey hairs, before (baseline,  
30 BL) and 0.5h, 1h and 2h after intrathecal or intraplantar administration of PD 198306 (1-30 $\mu$ g, i.t.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (10 $\mu$ g, i.t). For oral administration experiments, static allodynia was assessed

with von Frey hairs, before (baseline, BL) and 1h after oral administration of PD 198306 (3-30mg/kg, p.o.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (30mg/kg, p.o.). Animals were administered again the same compounds on the following day, both in the morning and the afternoon. Static allodynia was assessed before and 1h after the morning administration. In the afternoon static allodynia was assessed before, 1h, 2h and 3h after administration for streptozocin treated animals. CCI animals were assessed before, 1h and 2h after administration

#### 10 Drugs used

PD 198306 and pregabalin were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD 198306 was suspended in cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. Both compounds were administered orally, intrathecally or intraplantar in volumes of 1ml/kg, 10µl and 15 100µl respectively. Streptozocin (Aldrich, UK) was dissolved in 0.9% w/v NaCl and administered intraperitoneally in a volume of 1ml/kg.

#### Statistics

Data were analysed using a Kruskal-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test vs vehicle group.

### RESULTS

#### **1. Effects of PD 198306 on static allodynia, following systemic administration**

##### 25 1.1. Effect of PD198306 on streptozocin-induced static allodynia

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (3-30mg/kg, p.o) had no effect on streptozocin-induced static allodynia 1h after administration (FIG. 2).  
30 However, after the compound had been administered twice more on the following day, PD 198306 (30mg/kg) significantly blocked streptozocin-induced static allodynia for 2h after the third administration (FIG. 2).

### 1.2. Effect of PD198306 on CCI-induced static allodynia

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked CCI-induced static allodynia 1h after administration. In contrast, neither a single or  
5 multiple administration of PD 198306 (3-30mg/kg, p.o) had any effect on CCI-induced static allodynia (FIG. 3).

### **2. Effects of PD 198306 on static allodynia, following intrathecal administration**

10 Intrathecally administered PD198306 (1-30 $\mu$ g) dose-dependently blocked the maintenance of static allodynia in both streptozocin (FIG. 4) and CCI animals (FIG. 5) with respective MEDs of 3 and 10  $\mu$ g. This antiallodynic effect lasted for 1h.

### **3. Effects of PD 198306 on static allodynia, following intraplantar administration**

An intrathecal administration of PD 198306 (30 $\mu$ g) significantly blocked static allodynia in both neuropathic pain models (FIGS. 6,7). In contrast, a single  
20 administration of PD 198306 at a dose 100-fold higher (3mg/100 $\mu$ l) directly into the paw had no effect on streptozocin (FIG. 6) or CCI-induced static allodynia (FIG. 7).

### REFERENCES

Bennett GJ, Xie Y-K. A peripheral mononeuropathy in rat that produces  
25 disorders of pain sensation like those seen in man. Pain 1988;33:87-107.

Courteix C, Eschalier A and Lavarenne J. Streptozocin –induced rats: behavioural evidence for a model of chronic pain. Pain 1993;53:81-8

### Example 3

#### Effect of other MEK inhibitors in a neuropathic pain model in the rat

##### SUMMARY

5       The effect of several MEK inhibitors, with different binding affinities, has been investigated in the CCI model of neuropathic pain in the rat, by assessing static allodynia with von Frey hairs. Intrathecal administration of PD219622 or PD297447 (30µg) had no significant effect on allodynia. This lack of effect may reflect the low affinity or solubility of the compounds. However, 10 intrathecal administration of PD 254552 or PD 184352 (30µg), which possesses higher binding affinities, blocked the maintenance of static allodynia in CCI animals. The antiallodynic effect was only evident for 30min post-injection and thus, shorter than the one observed for pregabalin (100µg). The magnitude of the effect was similar for 30µg of PD 184352 and 100µg of pregabalin. From 15 this study it is concluded that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compounds.

20       The animals and methods for developing chronic constriction injury in the rat, injecting test compounds, and evaluation of static allodynia were according to Example 2 above. PD219622, PD297447, PD 184352, PD 254552 and pregabalin were administered intrathecally at doses of 30µg for all PD compounds and 100µg for pregabalin. Static allodynia was assessed with von Frey hairs, before (baseline, BL) and 0.5h, 1h and 2h after intrathecal 25 administration of the compounds

##### Drugs used

PD297447, PD219622, PD 254552, PD 184352 (CI-1040), and pregabalin were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD297447, 30 PD219622, PD 254552 and PD 184352 were suspended in cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. All compounds were administered intrathecally in a 10µl volume.

### Statistics

Data were analysed using a Kruskal-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test vs vehicle group.

5

### RESULTS

Intrathecally administered PD297447 or PD219622 (30 $\mu$ g) had no significant effect on allodynia. This lack of effect may reflect the low affinity of the compounds (965nM and 100nM respectively). However, intrathecal administration of PD 184352 or PD 254552 (30 $\mu$ g) blocked the maintenance of static allodynia in CCI animals (see FIG. 8). These compounds possess higher affinity (2 and 5 nM respectively). The antiallodynic effect was only evident for 30min post-injection and thus, shorter than the one observed for pregabalin (100 $\mu$ g). The magnitude of the effect was similar for 30 $\mu$ g of PD 184352 and 100 $\mu$ g of pregabalin.

15

The results indicate that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compounds.

## CHEMICAL EXAMPLES

### Example 1

5 Preparation of 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-  
difluoro-benzenesulfonamide (PD 0297447)

N-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide.

To a stirring suspension comprised of O-cyclopropylmethyl-  
hydroxylamine hydrochloride (5.40 g, 0.0437 mol) in dichloromethane (20 ml)  
10 at ambient temperature under a nitrogen atmosphere was added  
diisopropylethylamine (10.8 ml, 0.062 mol). A solution comprised of 2,3,4-  
trifluorobenzenesulfonyl chloride (Oakwood Products, Inc., 1.00 g,  $4.34 \times 10^{-3}$   
mol) in dichloromethane (120 ml) was added dropwise to the reaction vessel  
containing the stirring suspension over a 12 minute period. The reaction  
15 mixture was stirred for another 12 minutes and was quenched with 10 %  
aqueous hydrochloric acid (140 ml). The biphasic mixture was stirred  
vigorously for 16 hours. The layers were separated and the organic phase  
was dried ( $\text{MgSO}_4$ ) and concentrated to 6 ml volume. The concentrated  
solution was administered to a flash silica column (Biotage, 90 g of silica gel).  
20 Elution with dichloromethane afforded 0.8283 g of a white amorphous solid;  
68 % yield;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$  signal offset to  $\delta$  7.03; values reported  
are uncorrected)  $\delta$  7.50 (m, 1H), 7.10 (s, 1H), 6.95 (m, 1H), 3.59 (d, 2H,  $J=7.2$   
Hz), 0.80 (m, 1H), 0.31 (m, 2H), 0.02 (m, 2H);  $^{19}\text{F-NMR}$  (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -  
122.65 (m, 1F), -129.37 (m, 1F), -156.20 (m, 1F); MS (APCI-) 280 (M-1, 100),  
25 210 (55), 195 (45).

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-  
benzenesulfonamide (PD 0297447).

To a stirring solution comprised of 2-chloro-4-iodoaniline in  
30 tetrahydrofuran (10 ml) at  $-78^\circ\text{C}$  under a nitrogen atmosphere was added a  
1.0 M tetrahydrofuran solution of lithium *bis*trimethylsilylamide (6.2 ml,  $6.2 \times$   
 $10^{-3}$  mol) to form a green suspension. The suspension was stirred for five

minutes before a stirring suspension comprised of lithiated *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide (prepared by adding 3.0 ml of the 1.0 M lithium *b*is(trimethyl)silylamide solution to a stirring solution comprised of *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide in 10 ml of tetrahydrofuran at  $-78^{\circ}\text{C}$  under nitrogen gas) was added via canula. The cold bath was removed and the stirring suspension was stirred for one hour. The reaction mixture was quenched with 10 % aqueous hydrochloric acid (50 ml) and the biphasic mixture was concentrated *in vacuo* to an aqueous suspension that was extracted with diethyl ether (200 ml). The organic phase was dried ( $\text{MgSO}_4$ ) and was concentrated *in vacuo* to afford a tan oil. The crude product was purified by flash chromatography. Elution with a gradient (hexanes-ethyl acetate 99:1  $\rightarrow$  (2 min) 9:1  $\rightarrow$  (25 min) 3:1 afforded 1.10 g of a white amorphous foam; 73 % yield;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  7.69 (m, 1H), 7.59 (d, 1H,  $J=1.9$  Hz), 7.34 (dd, 1H,  $J=8.7, 1.9$  Hz), 7.27 (s, 1H), 7.00 (s, 1H), 6.95 (m, 1H), 6.43 (dd, 1H,  $J=8.7, 5.8$  Hz), 3.52 (d, 2H,  $J=7.5$  Hz), 0.74 (m, 1H), 0.34 (m, 2H), 0.02 (m, 2H);  $^{19}\text{F-NMR}$  (376 MHz;  $\text{CDCl}_3$ )  $\delta$   $-124.76$  (m, 1F),  $-136.69$  (d, 1F,  $J=18.3$  Hz); MS (APCI+) 515 ( $M+1$ , 100); (APCI-) 513 ( $M-1$ , 50), 443 (73), 428 (100); IR (KBr)  $1491\text{ cm}^{-1}$ ; Anal. Calcd/found for  $\text{C}_{16}\text{H}_{14}\text{ClF}_2\text{IN}_2\text{O}_3\text{S}$  C, 37.34/36.54; H, 2.74/2.71; N, 5.44/5.15; F, 7.38/7.57.

The APK  $\text{IC}_{50}$  for PD 0297447 is  $0.965\text{ }\mu\text{M}$ .

## EXAMPLE 1A

Preparation of 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitrobenzoic acid

5

Step a: Preparation of 5-nitro-2,3,4-trifluorobenzoic acid

To gently stirring concentrated sulfuric acid (50 ml) was added fuming nitric acid (3.4 ml, 0.076 mol). Solid 2,3,4-trifluorobenzoic acid (10.00 g, 0.05565 mol) was added directly in increments. After stirring 45 minutes, the reaction mixture had become an orange homogeneous solution which was then poured over chilled water (400 ml). The resulting aqueous suspension was extracted with diethyl ether (3 x 200 ml). The combined extracts were dried with anhydrous magnesium sulfate and concentrated *in vacuo* to yield 12.30 g of a dull, light-yellow solid. Recrystallization from chloroform (50 ml) afforded 9.54 g of the pale yellow microcrystalline product; 78 % yield; m.p. ; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 14.29 (broad s, 1H), 8.43-8.38 (m, 1H); <sup>13</sup>C-NMR (100 MHz; DMSO) δ 162.41, 154.24 (dd, J<sub>C-F</sub>=270.1, 10.7 Hz), 148.35 (dd, J<sub>C-F</sub>=267.0, 9.2 Hz), 141.23 (dt, J<sub>C-F</sub>=253.4 Hz), 133.95, 123.30 (d, J<sub>C-F</sub>=2.2 Hz), 116.92 (dd, J<sub>C-F</sub>=18.2, 3.8 Hz); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -120.50 to -120.63 (m), -131.133 to -131.27 (m), -153.63 to -153.74 (m).

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Step b: Preparation of 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitrobenzoic acid

To a stirring solution comprised of 2-chloro-4-iodoaniline (Lancaster, 98 %, 12.33 g, 0.04864 mol) in tetrahydrofuran (20 ml) at -78 °C under nitrogen was added a 2.0 M lithium diisopropylamide solution in tetrahydrofuran-heptane-ethylbenzene (Aldrich, 35 ml, 0.070 mol) with a syringe. The addition formed a thick suspension. After five minutes of stirring, a solution comprised of 5-nitro-2,3,4-trifluorobenzoic acid (5.00 g, 0.0226 mol) in tetrahydrofuran (30 ml) was added with a syringe to give a dark reaction mixture. The cold bath was removed and the reaction mixture stirred for 20 minutes. The cool reaction mixture was poured into ether (600 ml) containing an excess of

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hydrogen chloride. The red solution instantly turned to a yellow suspension as a precipitate formed. This precipitate was removed by vacuum filtration. The filtrate was concentrated *in vacuo* to a red powder (10.5 g). The red powder was triturated with boiling chloroform (800 ml). The triturated solids were collected by vacuum filtration to give an orange powder (2.42 g). The mother liquor from the trituration was concentrated *in vacuo* to give a red-orange solid (ca. 10 g undried). This solid was loaded onto a flash silica column. Elution with dichloromethane removed some impurities. Continuing elution with 1 % methanol in dichloromethane afforded ca. 4 g of a red solid.

This red solid was dissolved in hot absolute ethanol (100 ml). The solution was boiled down to 50 ml before dilution to 300 ml with hexanes. This solution was boiled to 150 ml and rediluted to 300 ml with hexanes to produce slight turbidity. The mixture was cooled in the refrigerator for three days, affording a yellow precipitate. The precipitate was collected by vacuum filtration and was dried with suction to afford 0.15 g of a yellow solid; 1 % yield;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  8.94 (s, 1H), 8.55 (s, 1H), 7.79 (d, 2H,  $J=2.0$  Hz), 7.61-7.57 (m, 2H), 6.90 (dd, 1H,  $J=8.5, 3.9$  Hz), 6.84 (dd, 1H,  $J=8.3, 6.6$  Hz);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$  -122.62 (s); MS (APCI+) 692 (6), 691 (8), 690 (31), 689 (10), 688 (55), 171 (47), 130 (100); (APCI-) 691 (4), 690 (12), 689 (14), 688 (70), 687 (32), 686 (100), 506 (50), 453 (97); IR (KBr)  $1523\text{ cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{19}\text{H}_{10}\text{Cl}_2\text{F}_2\text{N}_3\text{O}_4$  C, 33.17/33.32; H, 1.47/1.73; N, 6.11/5.73; Cl, 10.31/10.04; F, 2.76/3.70; I, 36.89/34.32.

The APK  $\text{IC}_{50}$  for 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitrobenzoic acid is 29.6 nM.

## EXAMPLE 1B

4-Fluoro-2-(4-methanesulfanyl-phenylamino)-benzoic acid (1).

- To a solution of 4-(methylmercapto)aniline (3.1622 g, 0.02 mole) in
- 5 THF at  $-78^{\circ}\text{C}$ , a solution of LDA in THF (2M, 30 ml, 0.06 mole) was added and the reaction mixture stirred for 30 minutes at  $-78^{\circ}\text{C}$  (Scheme 1E). Solid 2,4-difluoro benzoic acid (3.1622 g, 0.02 mole) was added and the reaction stirred for 16 hours while it warmed up to room temperature. The reaction
- 10 mixture was poured into ether saturated with HCl gas. HCl gas was bubbled into until precipitation of salts ceased. The precipitated salts were separated by filtration and discarded. The ether layer was concentrated to give **1** as a white solid. Yield 5.63 g (100%); mp  $173-179^{\circ}\text{C}$  (DEC);  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.39 (s, 1H), 8.04 (dd, 1H,  $J=9.2, 6.8$  Hz), 7.32-7.17 (AB quartet, 4H), 6.74 (dd, 1H,  $J=12.1, 2.4$  Hz), 6.46-6.41 (m, 1H), 2.51 (s, 3H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )  $\delta$  172.79, 167.57 (d,  $J_{\text{C-F}}=253.4$  Hz), 151.55 (d,  $J_{\text{C-F}}=12.2$  Hz), 136.83, 135.40 (d,  $J_{\text{C-F}}=12.2$  Hz), 134.72, 128.31, 124.60, 106.51, 105.12 (d,  $J_{\text{C-F}}=22.9$  Hz), 99.79 (d,  $J_{\text{C-F}}=26.7$  Hz), 16.51;  $^{19}\text{F-NMR}$  (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -101.39 to -101.46 (m); MS (APCI+) 278 ( $M+1$ , 100); IR (KBr) 3319, 1664,
- 20 1589,  $1258\text{ cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{14}\text{H}_{12}\text{FNO}_2\text{S}$  C, 60.64/60.99; H, 4.36/4.63; N, 5.05/4.80; S, 11.56/10.97.

## EXAMPLE 2B

4-Fluoro-2-(4-methanesulfinyl-phenylamino)-benzoic acid (2).

- 25 A mixture of **1** (Scheme 1B) (0.286 g, 0.001031 mole) and oxaziridine (0.235 g, 0.0009 mole) in  $\text{CHCl}_3$  (30 ml) at room temperature for 2 hours. The solvent was removed and the resulting brown oil chromatographed on silica column. Elution with  $\text{CH}_2\text{Cl}_2$  removed fast moving byproduct. Further elution with  $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$  (9.5:0.5),  $R_f = 0.27$ , gave pure **2** as a light brown solid.
- 30 Yield 132.8 mg (50%); mp  $191-192^{\circ}\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.77 (s, 1H), 8.08 (dd, 1H,  $J=8.9, 6.7$  Hz), 7.70-7.39 (AB quartet, 4H), 6.98 (dd, 1H,  $J=11.6, 2.4$  Hz), 6.57-6.52 (m, 1H), 2.80 (s, 3H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )  $\delta$  170.76, 167.18 (d,  $J_{\text{C-F}}=253.3$  Hz), 149.33 (d,  $J_{\text{C-F}}=12.2$  Hz), 143.02, 139.50,

135.37 (d,  $J_{C-F}=12.2$  Hz), 125.47, 122.32, 108.22, 106.35 (d,  $J_{C-F}=22.8$  Hz), 100.69, (d,  $J_{C-F}=25.9$  Hz), 43.75; MS (APCI+) 294 (M+1, 100); IR (KBr) 1673, 1592, 1228  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{14}\text{H}_{12}\text{FNO}_3\text{S}$  C, 57.33/57.48; H, 4.12/4.27; N, 4.78/4.67.

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### EXAMPLE 3B

#### 4-Fluoro-2-(4-methanesulfonyl-phenylamino)-benzoic acid (3).

A solution of **1** (Scheme 1B) (0.4458 g, 0.00152 mole) and tetrabutylammonium oxon (1.1 g, 0.0030 mole) in  $\text{CH}_2\text{Cl}_2$  (20 ml) was stirred at room temperature for 16 hours. TLC showed the presence of starting material; so additional 1.1 g (0.0030 mole) of the tetrabutylammonium oxon was added and reaction mixture stirred for 16 more hours. The reaction mixture was loaded on to a silica column and eluted with  $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$  (9.75:0.25) and the fast moving fraction collected and concentrated to give **3** as a white solid.

Yield, 0.3856 g (82%); mp 200-202 °C;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.78 (s, 1H), 8.13 (dd, 1H,  $J=8.9, 6.5$  Hz), 7.94-7.38 (AB quartet, 4H), 7.10 (dd, 1H,  $J=11.3, 2.4$  Hz), 6.66-6.61 (m, 1H), 3.09 (s, 3H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )  $\delta$  171.52, 167.28 (d,  $J_{C-F}=254.9$  Hz), 148.32, 145.21, 135.59 (d,  $J_{C-F}=11.5$  Hz), 134.50, 129.39, 120.62, 108.74, 107.46 (d,  $J_{C-F}=22.8$  Hz), 101.61 (d,  $J_{C-F}=26.7$  Hz), 44.78;  $^{19}\text{F-NMR}$  (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -100.29 to -100.45 (m); MS (APCI+) 310 (M+1, 100); (APCI-) 308 (M-1, 100); Anal. calcd/found for:  $\text{C}_{14}\text{H}_{12}\text{FNO}_4\text{S} \cdot 0.75 \text{ H}_2\text{O}$  C, 52.08/52.36; H, 4.22/3.88; N, 4.34/4.26.

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### EXAMPLE 4B

#### 2-methyl-4-trimethylsilyl-ethynyl-aniline (5)

To a solution of 4-iodo-2-methyl-aniline (2.33g, 10 mmol), bis(triphenylphosphine)palladium(II)chloride (1.4g, 0.2 mmol), CuI (0.19 g, 0.1 mmol) in  $\text{Et}_3\text{N}$  (40 ml) at ice-bath temperature, (trimethylsilyl)acetylene (1.18 g, 12 mmol) was added dropwise (Scheme 2B). After an hour stirring, the ice-bath was removed and the reaction mixture heated at 40°C (oil-bath temperature) for one hour; cooled to room temperature and the solvent removed. The residue was partitioned between  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$

layer was separated, dried ( $\text{MgSO}_4$ ) and concentrated to give an oil. The oil was purified by silica column, eluting with  $\text{CH}_2\text{Cl}_2$ . The fraction with  $R_f = 0.37$  was collected and concentrated to give 2-methyl-4-trimethylsilanylethynylaniline as a dark brown oil.

5 Yield 1.50 g (83%).

#### EXAMPLE 5B

##### 4-Fluoro-2-(2-methyl-4-trimethylsilanylethynyl-phenylamino)-benzoic acid (6)

Continuing after Example 4B, to a solution of 2-methyl-4-trimethylsilanylethynylaniline (1.50 g, 0.008 mole) in THF (10 ml) at  $-78^\circ\text{C}$ , LDA (2 M in THF, 6 ml, 0.012 mole) was added and the mixture was stirred at  $-78^\circ\text{C}$  for 30 minutes. Solid 2,4-difluoro-benzoic acid (0.633 g, 0.004 mole) was added and the stirred for 16 hours while it warmed up to room temperature. The solvents were removed and water (30 ml) and  $\text{Et}_2\text{O}$  (50 ml) added to the oil residue. The mixture was stirred vigorously and the  $\text{Et}_2\text{O}$  layer separated, dried ( $\text{MgSO}_4$ ) and concentrated to give a brown solid. The solid was purified on silica column, eluted with  $\text{CH}_2\text{Cl}_2$ . The fraction with  $R_f = 0.37$  was collected and concentrated to give a light brown solid. The solid was added to pentane; some insoluble brown particulate was separated by filtration and discarded.

20 The pentane layer was concentrated to give **6** as a light yellow solid. Yield 0.65 g (47%); mp  $170-171^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  9.33 (s, 1H), 8.05 (dd, 1H,  $J=8.9, 6.8$  Hz), 7.43 (d, 1H,  $J=1.2$  Hz), 7.35 (dd, 1H,  $J=8.2, 1.7$  Hz), 7.25 (d, 1H,  $J=8.2$  Hz), 6.53 (dd, 1H,  $J=11.8, 2.4$  Hz), 6.47-6.42 (m, 1H), 2.25 (s, 3H), 0.26 (s, 9H);  $^{13}\text{C-NMR}$  (100 MHz;  $\text{CDCl}_3$ )  $\delta$  172.86, 167.61 (d,  $J_{\text{C-F}}=253.3$ ), 151.24 (d,  $J_{\text{C-F}}=12.3$  Hz), 138.28, 135.38 (d,  $J_{\text{C-F}}=11.4$  Hz), 134.85, 132.82, 130.63, 123.81, 119.91, 106.63, 105.23 (d,  $J_{\text{C-F}}=22.8$  Hz), 104.77, 99.98 (d,  $J_{\text{C-F}}=26.7$  Hz), 94.05, 17.78, 0.00; MS (APCI+) 342 ( $\text{M}+1$ , 100); IR (KBr) 2151, 1661, 1249  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{19}\text{H}_{20}\text{FNO}_2\text{Si}$  C, 66.83/67.02; H, 5.90/6.00; N, 4.10/4.09; F, 5.56/5.45.

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## EXAMPLE 6B

4-Fluoro-2-(2-methyl-4-ethynyl-phenylamino)-benzoic acid (7).

To a solution of **6** in CH<sub>3</sub>OH (30 ml), aqueous 1N KOH (10 ml) was added. After stirring at room temperature for 16 hours, the CH<sub>3</sub>OH was removed and the aqueous layer was acidified with 6N HCl (Scheme 2B). The resulting white precipitation was extracted in to Et<sub>2</sub>O, the Et<sub>2</sub>O layer was dried (MgSO<sub>4</sub>) and concentrated to give **7** as tan colored solid. Yield 0.4274 g (91%); mp 177-178 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 9.35 (s, 1H), 8.08-8.04 (m, 1H), 7.44 (s, 1H), 7.38-7.25 (m, 2H), 6.57 (d, 1H, J=11.8 Hz), 6.48-6.44 (m, 1H), 3.08 (s, 1H), 2.27 (s, 3H); <sup>13</sup>C-NMR (100 MHz; CDCl<sub>3</sub>) δ 172.84, 167.61 (d, J<sub>C-F</sub>=253.3), 151.15 (d, J<sub>C-F</sub>=12.3 Hz), 138.63, 135.40 (d, J<sub>C-F</sub>=12.3 Hz), 135.00, 132.87, 130.81, 123.76, 118.79, 106.75, 105.33 (d, J<sub>C-F</sub>=22.8 Hz), 100.03 (d, J<sub>C-F</sub>=26.0 Hz), 83.37, 17.83, 0.00; <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -101.24 to -101.31 (m); MS (APCI+) 270 (M+1, 100); IR (KBr) 3315, 1672, 1594, 1253 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>16</sub>H<sub>12</sub>FNO<sub>2</sub> C, 71.37/71.08; H, 4.49/4.82; N, 5.20/5.09.

## EXAMPLE 7B

1-(4-nitro-phenyl)-1H-pyrrole (9a)

To a gently refluxing mixture of 4-nitroaniline (6.906 g, 0.05 mole), and sodium acetate (23 g, 0.28 mole) in acetic acid (100 ml) was added 2,5-dimethoxytetrahydrofuran (7.26 g, 7.12 ml, 0.055 mole) dropwise (Scheme 3B). After refluxing for 3 hours, the reaction mixture was poured on to crushed ice (~250 ml), basified with 10 % sodium hydroxide (250 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried (K<sub>2</sub>CO<sub>3</sub>) to afford the product as a dark brown oil. Yield 9.40 g (100 %).

## EXAMPLE 8B

1-(4-nitro-phenyl)-1H-pyrazole (9b)

A mixture of pyrazole (6.808 g, 0.1 mole) tetrabutylammonium bromide (3.22 g, 0.01 mole) and KOH (11.22 g, 0.2 mole) were ground together and sonicated for 16 hours. To this 1-fluoro-4-nitrobenzene (15.521 g, 11.67 ml,

0.11 mole) was added and the mixture sonicated for 24 hours. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried (MgSO<sub>4</sub>) and concentrated to give dark brown solid. This was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> (R<sub>f</sub> = 0.44) gave the product as a light brown solid. Yield 8.80 g (47 %); mp 171-172 °C; Anal. calcd/for: C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub> C, 57.14/56.52; H, 3.73/3.62; N, 22.21/21.95.

#### EXAMPLE 9B

##### 3,5-dimethyl-1-(4-nitro-phenyl)-1H-pyrazole (9c)

To a solution of 4-nitro-phenyl-hydrazine (15.3 g, 0.1 mole) and 2,4-pentanedione (10.01 g, 10.27 ml, 0.1 mole) in EtOH (200 ml) were added 5 drops of concentrated HCl. The mixture was refluxed for 15 minutes; and the solvent removed to give a gummy product. This was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> gave the desired product (R<sub>f</sub> = 0.10) as a brown solid. Yield 7.22 g (33 %).

#### EXAMPLE 10B

##### 4-Pyrrol-1-yl-phenylamine (10a)

Catalytic reduction (H<sub>2</sub>/RaNi (5 g) /THF) of 1-(4-nitro-phenyl)- 1H-pyrrole (9.69 g, 0.05149 mole) at 51 psi gave crude product as an oil (Scheme 3B). The product was purified by silica column chromatography. Elution with CH<sub>2</sub>Cl<sub>2</sub> (R<sub>f</sub> = 0.13) gave the pure product as white solid. Yield 8.06 g (99 %); mp 80-81 °C.

#### EXAMPLE 11B

In a manner similar to the preparation of 4-pyrrol-1-yl-phenylamine, the following were prepared:

4-1H-Pyrazol-1-yl-phenylamine (10b). Dark brown oil, yield 6.26 g (100 %).

Benzenamine, 4-(3,5-dimethyl-1H-pyrazol-1-yl) (10c). Dark brown oil.

Yield 6.45 g (100 %).

#### EXAMPLE 12B

##### 4-Fluoro-2-(4-pyrrol-1-yl-phenylamino)-benzoic acid (11a)

- 5 To a solution of 4-pyrrol-1-yl-phenylamine (3.16 g, 0.02 mole) in THF (30 ml) at  $-78^{\circ}\text{C}$ , a solution of LDA (2M, 15 ml, 0.03 mole) was added and the mixture stirred for 30 minutes. Solid 2,4-difluorobenzoic acid was added and the reaction mixture stirred for 16 hours as it warmed up to room temperature. The solvent was removed and ether (100 ml) added to the dark oily residue.
- 10 This was stirred vigorously and the insoluble gummy precipitate separated by filtration. The gummy residue was dissolved in  $\text{H}_2\text{O}$ , acidified to pH 1 with 10% HCl, and extracted with  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$  layer was dried ( $\text{MgSO}_4$ ) and concentrated to give the target compound as a brown solid. Yield 2.74 g (93 %); mp  $223-225^{\circ}\text{C}$  (DEC);  $^{19}\text{F}$ -NMR (376 MHz;  $\text{CDCl}_3$ )  $\delta$  -101.44 (s); MS
- 15 (APCI+) 297 (M+1, 100); IR (KBr) 1658, 1526,  $1254\text{ cm}^{-1}$ .

In a manner similar to the preparation of 4-Fluoro-2-(4-pyrrol-1-yl-phenylamino)-benzoic acid, the following were prepared:

- 20 4-Fluoro-2-(4-pyrazol-1-yl-phenylamino)-benzoic acid (11b). Light brown solid, mp  $212-213^{\circ}\text{C}$ .

- 2-[4-(3,5-Dimethyl-pyrazol-1-yl)-phenylamino]-4-Fluoro benzoic acid (11c). Tan powder, mp  $198-200^{\circ}\text{C}$ .

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## EXAMPLE 1C

Preparation of 2-(2-chloro-4-iodo-phenylamino)-5-dimethylsulfamoyl-3,4-difluoro-benzoic acid methyl ester (APK IC<sub>50</sub>=222 nM)

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Step a: Preparation of 1-dimethylsulfamoyl-2,3,4-trifluorobenzene

To a gently stirring solution comprised of 2,3,4-trifluorobenzenesulfonyl chloride (5.70 g, 0.0247 mol) in 1,2-dichloroethane (200 ml) was introduced by bubbling gaseous anhydrous dimethylamine. The mixture became cloudy  
10 after several minutes and was subsequently washed with water (200 ml), 6 N aqueous hydrochloric acid (200 ml), brine (200 ml), was dried over anhydrous magnesium sulfate, and was concentrated *in vacuo* to obtain a yellow oil. The crude product was purified by flash chromatography. Elution with dichloromethane afforded 3.40 g of a white solid; 58 % yield; <sup>1</sup>H-NMR (400  
15 MHz; CDCl<sub>3</sub>) δ 7.63-7.56 (m, 1H), 7.12-7.04 (m, 1H), 2.812 (s, 3H), 2.807 (s, 3H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -124.91 to -125.03 (m), -127.98 to -128.03 (m), -156.41 to -156.53.

20

Step b: Preparation of 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid

To a cold (-78 °C) stirring solution comprised of 1-dimethylsulfamoyl-2,3,4-trifluorobenzene in anhydrous tetrahydrofuran (60 ml) under a nitrogen atmosphere was added a commercially available lithium diisopropylamide solution (Aldrich, 2.0 M in tetrahydrofuran/heptane/ethylbenzene, 7.5 ml, 0.0150 mol). After stirring for about ten minutes, the purple solution was  
25 transferred via canula to a cold, stirring, saturated carbon dioxide in diethyl ether solution (200 ml). The reaction mixture took on a dull burgundy color. The cold bath was removed and the reaction mixture warmed to ambient temperature over one hour. The mixture was then carefully quenched with 10 % aqueous hydrochloric acid (200 ml). The layers were separated. The  
30 organic phase was extracted twice (200, 100 ml portions) with 10 % (wt.) aqueous sodium hydroxide. The combined aqueous alkaline extracts were treated with concentrated aqueous hydrochloric acid (100 ml) to pH 0. A white precipitate formed. The suspension was allowed to cool, then was extracted with diethyl ether (600 ml). The organic extract was dried over  
35 anhydrous magnesium sulfate and was concentrated *in vacuo* to afford 2.70 g



of an off-white solid; 67.5 % yield; mp 225-228 °C; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 14.08 (broad s, 1H), 8.02-7.97 (m, 1H), 2.75 (s, 3H), 2.74 (s, 3H) <sup>19</sup>F-NMR (376 MHz; DMSO) δ -122.50 to -122.63 (m), -122.95 to -123.08 (m), -154.49 to -154.61 (m); MS (APCI+) 284 (M+1, 22), 238 (100); (APCI-) 282 (M-1, 85), 259 (94), 238 (46), 216 (91), 195 (100); IR (KBr) 1702 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>9</sub>H<sub>8</sub>F<sub>3</sub>NO<sub>4</sub>S C, 38.17/38.40; H, 2.85/2.90; N, 4.95/4.80; F, 20.12/19.75; S, 11.32/11.12.

10 Step c: Preparation of 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid methyl ester

The solid 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid (1.47 g, 0.00519 mol) and *p*-toluenesulfonic acid catalyst (17.1 mg) were dissolved in methanol (125 ml). The stirring mixture was brought to reflux under a nitrogen atmosphere for 51 hours. The reaction mixture was concentrated *in vacuo* to give a solid. The product was partitioned between diethyl ether (200 ml) and saturated aqueous potassium carbonate (75 ml). The layers were separated and the organic phase was washed with water (75 ml), brine (75 ml), was dried over anhydrous potassium carbonate, and was concentrated *in vacuo* to afford 0.15 g of an off-white solid; 10 % yield; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 8.23-8.19 (m, 1H), 3.92 (s, 3H), 2.83 (s, 6H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -120.79 to -121.02 (m), -153.69 to -153.80.

25 Step d: Preparation of 2-(2-chloro-4-iodo-phenylamino)-5-dimethylsulfamoyl-3,4-difluoro-benzoic acid methyl ester

To a stirring cold (-78 °C) solution comprised of 2-chloro-4-iodoaniline (0.143 g, 5.64x10<sup>-4</sup> mol) in anhydrous tetrahydrofuran (5 ml) under a nitrogen atmosphere was added a commercially available lithium diisopropylamide solution (Aldrich, 2.0 M in tetrahydrofuran/heptane/ethylbenzene, 0.300 ml, 6.0x10<sup>-4</sup> mol). After stirring for 5 minutes, a solution comprised of 5-dimethylsulfamoyl-2,3,4-trifluoro-benzoic acid methyl ester (0.15 g, 5.0x10<sup>-4</sup> mol) in tetrahydrofuran (10 ml) was added via syringe. The cold bath was removed and the reaction mixture was stirred for 2 hours. The reaction mixture was then partitioned between diethyl ether (125 ml) and saturated aqueous sodium bicarbonate (125 ml). The aqueous bicarbonate phase was

extracted with an additional portion (125 ml) of diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The oil was crystallized from heptane-ethyl acetate to afford 0.060 g of an off-white powder; 23 % yield; mp  
5 154-156 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 9.74 (s, 1H), 8.30 (d, 1H, J=7.1 Hz), 7.72 (s, 1H), 7.49 (d, 1H, J=8.3 Hz), 6.73-6.69 (m, 1H), 3.92 (s, 3H), 2.84 (s, 3H), 2.83 (s, 3H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -123.90 (d), -139.55 (d).

### EXAMPLE 2C

10

Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-benzamide (PD 219622)

15

Step a: Preparation of 1-bis-(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzene

20

To a stirring solution comprised of *bis*-4-methoxybenzylamine (2.5 g, 9.7x10<sup>-3</sup> mol) and diisopropylethylamine (1.7 ml, 9.7x10<sup>-3</sup> mol) in dichloromethane (50 ml) at

25

0 °C under nitrogen atmosphere was added liquid 2,3,4-trifluorobenzenesulfonyl chloride (2.26 g, 9.5x10<sup>-3</sup> mol) directly. The mixture was stirred cold for ten minutes. The ice-water bath was removed and the mixture was stirred for an additional 15 minutes and was then diluted with dichloromethane to 350 ml volume and was washed with saturated aqueous ammonium chloride (200 ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford 4.99 g of a sticky white solid. The crude product was recrystallized from hexanes-acetone to afford 3.00 g of white needles; 70 % yield; mp 87-90 °C; <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>) δ 7.64-7.58 (m, 1H), 7.04-6.99 (m, 1H), [6.97 (d, 4H, J=8.5 Hz), 6.75 (d, 4H, J=8.8 Hz) AB q], 4.33

30

(s, 4H), 3.76 (s, 6H); <sup>19</sup>F-NMR (376 MHz; CDCl<sub>3</sub>) δ -125.44 to -125.56 (m), -128.61 to -128.72 (m), -156.91 to -157.03 (m); MS (APCI+) 121 (M-330, 100); (APCI-) 330 (M-121, 18), 195 (M-256, 100); IR (KBr) 1612, 1517, 1506, 1465, 1258, 1240, 1156, 1037, 1030 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>22</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>4</sub>S C, 58.53/57.98; H, 4.47/4.61; N, 3.10/2.85.

35

Step b: Preparation of 5-bis-(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoic acid

To a stirring solution comprised of 1-bis-(4-methoxybenzyl)sulfamoyl-  
 5 2,3,4-trifluorobenzene (2.95 g,  $6.5 \times 10^{-3}$  mol) in tetrahydrofuran (60 ml) at  $-78$  °C was added a solution comprised of 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich, 3.35 ml,  $6.7 \times 10^{-3}$  mol). After several minutes of stirring, the dark solution was transferred via canula over five minutes to a stirring solution comprised of carbon dioxide (excess) in  
 10 diethyl ether at  $-78$  °C. A white precipitate immediately formed. The cold bath was removed and the reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was quenched with 200 ml of dilute aqueous hydrochloric acid. The layers were separated and the organic phase was dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give 2.82 g of an off-  
 15 white solid. Recrystallization from dichloromethane (150 ml) afforded 2.10g of the white powder product; 65 % yield; mp  $158-161$  °C;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  7.80-7.76 (m, 1H), 7.05-6.74 (AB q, 8H,  $J=8.6$  Hz), 4.33 (s, 4H), 3.66 (s, 6H);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$   $-123.28$  to  $-123.36$  (m),  $-124.12$  to  $-124.21$  (m),  $-155.41$  to  $-155.53$  (m); MS (APCI-) 494 (M-1, 47), 216 (89),  
 20 195 (100); IR (KBr) 3420, 2954, 2838, 1695, 1613, 1512, 1347, 1238, 1152, 1079  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{23}\text{H}_{20}\text{F}_3\text{NO}_6\text{S}$  C, 55.76/55.85; H, 4.07/4.02; N, 2.83/2.71; F, 11.50/11.41; S, 6.47/6.25.

25 Step c: Preparation of 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (PD 215729)

To a stirring solution comprised of 2-chloro-4-iodoaniline (0.53 g,  $2.0 \times 10^{-3}$  mol) in tetrahydrofuran (10 ml) at  $-78$  °C under a nitrogen atmosphere was added a solution comprised of 1.0 M lithium bis(trimethylsilyl)amide in tetrahydrofuran (Aldrich, 4.1 ml,  $4.1 \times 10^{-3}$  mol).  
 30 Within several minutes the solution became a thick light-green suspension. To this mixture was added a solution comprised of lithium 5-bis-(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoate in tetrahydrofuran, which was prepared by adding 2.0 ml of the Aldrich lithium bis(trimethylsilyl)amide solution (0.0020 mmol) to a solution comprised of 5-bis-(4-

methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoic acid (1.00 g,  $2.0 \times 10^{-3}$  mol) in tetrahydrofuran (10 ml) at  $-78^\circ\text{C}$ . The reaction mixture was stirred for 15 minutes and was then concentrated *in vacuo* to a crude semisolid. The semisolid was taken up into diethyl ether (250 ml) and was washed with 1 % aqueous hydrochloric acid (150 ml). The ether phase was then washed with neutral water (200 ml, pH 4 after wash), a second portion of water (200 ml, pH 6 after wash), and brine (200 ml). The organic phase was then dried ( $\text{MgSO}_4$ ) and was concentrated *in vacuo* to give 1.88 g of a sticky residue which was crystallized from toluene-heptane to afford 1.12 g of an off-white powder; 76 % yield; mp  $162-166^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  9.86 (s, 1H), 7.92 (d, 1H,  $J=6.8$  Hz), 7.86 (d, 1H,  $J=1.7$  Hz), 7.60 (dd, 1H,  $J=8.5, 1.7$  Hz), 7.06-7.04/6.78-6.75 (AB q, 8H,  $J=8.5$  Hz), 6.93-6.89 (m, 1H), 4.31 (s, 4H), 3.66 (s, 6H);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$   $-127.22$  (d),  $-141.36$  (d); MS (APCI+) 729 (M+1, 1), 256 (50), 121 (100); (APCI-) 727 (M-1, 100); IR (KBr) 1698, 1673, 1513,  $1251\text{ cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{29}\text{H}_{24}\text{ClF}_2\text{IN}_2\text{O}_6\text{S}$  C, 47.78/47.93; H, 3.32/3.33; N, 3.84/3.80; Cl, 4.86/4.84; F, 5.21/5.46; I, 17.41/17.16; S, 4.40/4.29.

Step d: Preparation of 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD 218774)

To a stirring solution comprised of 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (0.935 g,  $1.28 \times 10^{-3}$  mol), cyclopropylmethoxylamine hydrochloride (0.175 g,  $1.42 \times 10^{-3}$  mol), and diisopropylethylamine (0.75 ml,  $4.26 \times 10^{-3}$  mol) in a 1:1 v/v tetrahydrofuran-dichloromethane mixture (50 ml) was added solid PyBOP ([benzotriazolyl]tripyrrolidino phosphonium hexafluorophosphate, Advanced ChemTech, 0.76 g,  $1.46 \times 10^{-3}$  mol). The reaction mixture was stirred for one hour, was then evaporated to a crude residue which was purified by flash silica column chromatography. Elution with a gradient (25 % dichloromethane to 75 % dichloromethane in hexanes) afforded 0.63 g of the off-white powder product; 62 % yield; mp  $70-300^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  11.92 (s, 1H), 9.35 (s, 1H), 7.60 (s, 1H), 7.50-7.45 (m, 1H), 7.34 (d, 1H,  $J=8.5$  Hz), 6.82-6.54 (AB q, 8H,  $J=8.3$  Hz), 6.59-6.54 (m, 1H), 4.09 (s,

4H), 3.46 (s, 6H), 0.90-0.80 (m, 1H), 0.30-0.25 (m, 2H), 0.03-0.00 (m, 2H);  
<sup>19</sup>F-NMR (376 MHz; DMSO) δ -129.05 (s), -140.23 (d, J=18.3 Hz); MS  
 (APCI+) 798 (M+1, 70); (APCI-) 796 (M-1, 15), 726 (50), 131 (100); IR (KBr)  
 1642, 1611, 1584, 1513, 1478 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>33</sub>H<sub>31</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>6</sub>S  
 5 C, 49.67/49.88; H, 3.92/3.95; N, 5.27/5.19.

Step e: Preparation of 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-benzamide (PD 219622)

A reaction solution comprised of 5-bis-(4-methoxybenzyl)sulfamoyl-2-  
 10 (2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide  
 (0.1010 g, 1.266x10<sup>-4</sup> mol) in trifluoroacetic acid (4 ml) was stirred at ambient  
 temperature for 24 hours. The mixture was vacuum filtered and the  
 precipitate rinsed with hexanes to afford 28.6 mg of a pale lavender powder;  
 42 % yield; mp 219-227 °C DEC; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 11.89 (s, 1H),  
 15 9.08 (s, 1H), 7.60 (s, 3H), 7.55 (d, 1H, J=6.9 Hz), 7.32 (d, 1H, J=8.6 Hz), 6.63-  
 6.59 (m, 1H), 3.40 (d, 2H, J=6.6 Hz), 0.90-0.80 (m, 1H), 0.30-0.26 (m, 2H),  
 0.05-0.00 (m, 2H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ  
 -130.61 (s), -140.38 (d, J=21.4 Hz); MS (APCI+) 558 (M+1, 70), 282 (100);  
 (APCI-) 556 (M-1, 73), 486 (100); IR (KBr) 3390, 3283, 1652, 1513, 1477,  
 20 1163 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>17</sub>H<sub>15</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>4</sub>S · 0.1 C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub> C,  
 36.30/36.31; H, 2.67/2.55; N, 7.38/7.00.

### EXAMPLE 3C

25 Preparation of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-5-sulfamoyl-benzamide (PD 224213)

To a stirring solution comprised of 5-bis-(4-methoxybenzyl)sulfamoyl-2-  
 (2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (0.67 g, 9.2x10<sup>-4</sup> mol),  
 O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.113 g, 9.65x10<sup>-4</sup> mol), and  
 30 diisopropylethylamine (0.50 ml, 2.9x10<sup>-3</sup> mol) in a 1:1 v/v tetrahydrofuran-  
 dichloromethane mixture (20 ml) was added solid PyBOP  
 ([benzotriazolyloxy]tripyrrolidino phosphonium hexafluorophosphate,  
 Advanced ChemTech, 0.52 g, 1.0x10<sup>-3</sup> mol). The reaction mixture was stirred  
 for 30 minutes, was concentrated *in vacuo* to a yellow oil, and was crystallized  
 35 from methanol to afford 0.35 g of the off-white amorphous intermediate; 46 %

yield; the intermediate was dissolved in trifluoroacetic acid (10 ml) and was stirred at ambient temperature for 16 hours. The mixture was vacuum filtered to collect the precipitate, which was recrystallized from methanol-chloroform to afford 0.055 g of the tan powder product; 26 % yield from intermediate; mp 230-236 °C DEC; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 11.73 (s, 1H), 9.46 (s, 1H), 9.38 (s, 1H), 7.80-7.75 (m, 2H), 7.79 (s, 2H), 7.50 (d, 1H, J=8.5 Hz), 6.82-6.78 (m, 1H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -130.83 (s), -139.24 (s); MS (APCI+) 504 (M+1, 53), 488 (90), 471 (100); (APCI-) 502 (M-1, 12), 486 (100); IR (KBr) 3295, 1652, 1636, 1519, 1477, 1315, 1157 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>13</sub>H<sub>9</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>4</sub>S 0.41 CHCl<sub>3</sub> C, 29.15/29.05; H, 1.72/1.66; N, 7.60/7.21.

#### EXAMPLE 4C

Preparation of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-sulfamoyl-benzoic acid (PD 215730)  
Solid 5-bis-(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid (0.0995 g, 1.36x10<sup>-4</sup> mol) was dissolved in trifluoroacetic acid (5 ml) under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 65 hours. The mixture was vacuum filtered to isolate 55.2 mg of a fine white precipitate. The crude product was recrystallized from chloroform to afford 31.8 mg of the fluffy white solid product; 48 % yield; mp 295-296 °C DEC; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 9.77 (s, 1H), 8.16 (d, 1H, J=7.3 Hz), 7.82 (s, 3H), 7.56 (d, 1H, J=8.5 Hz), 6.97-6.92 (m, 1H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -128.47 (s), -141.13 (d, 19.8 Hz); MS (APCI+) 489 (M+1, 5), 102 (100); (APCI-) 491 (32), 490 (18), 489 (100), 488 (18), 487 (M-1, 75); IR (KBr) 3372, 3244, 1688 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>13</sub>H<sub>8</sub>ClF<sub>2</sub>IN<sub>2</sub>O<sub>4</sub>S C, 31.96/32.19; H, 1.65/1.81; N, 5.73/5.37.

#### EXAMPLE 5C

Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-benzamide (PD 250253)

Step a: Preparation of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-dimethylsulfamoyl-benzoic acid (PD 224339)

To a stirring solution comprised of 5-dimethylsulfamoyl-2,3,4-trifluorobenzoic acid (1.00 g,  $3.53 \times 10^{-3}$  mol) in tetrahydrofuran (15 ml) at  $-78^\circ\text{C}$  under a nitrogen atmosphere was added a 1.0 M solution of lithium *bis*(trimethylsilyl)amide in tetrahydrofuran (Aldrich, 3.6 ml,  $3.6 \times 10^{-3}$  mol). A lithium 2-chloro-4-iodoanilide suspension formed by adding a 1.0 M solution of lithium *bis*(trimethylsilyl)amide solution (7.2 ml,  $7.2 \times 10^{-3}$  mol) to a solution comprised of 2-chloro-4-iodoaniline (0.94 g,  $3.63 \times 10^{-3}$  mol) in tetrahydrofuran (15 ml) at  $-78^\circ\text{C}$  was added via canula to the lithium 5-dimethylsulfamoyl-2,3,4-trifluorobenzoate suspension. The cold bath was removed and the reaction mixture was stirred for one hour. The mixture was concentrated *in vacuo* to a crude solid. The crude product was suspended in diethyl ether (200 ml), to which suspension hydrogen chloride gas was introduced to produce a white precipitate. The precipitate was removed by vacuum filtration. The filtrate was concentrated *in vacuo* to give a dull-colored solid, which was triturated with hexanes-dichloromethane to afford 1.31 g of the white powder product; 72 % yield; mp  $218-222^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz; DMSO)  $\delta$  9.89 (s, 1H), 8.06 (d, 1H,  $J=6.1$  Hz), 7.85 (d, 1H,  $J=1.9$  Hz), 7.58 (dd, 1H,  $J=8.5, 1.9$  Hz), 7.03 (dd, 1H,  $J=8.3, 6.6$  Hz), 2.71 (s, 6H);  $^{19}\text{F-NMR}$  (376 MHz; DMSO)  $\delta$   $-125.58$  (d,  $J=18.3$  Hz),  $-140.14$  (d,  $J=16.8$  Hz); MS (APCI+) 519 (40), 518 (15), 517 ( $M+1$ , 100); (APCI-) 517 (6), 516 (2), 515 ( $M-1$ , 5), 480 (45), 127 (100); IR (KBr) 3346, 1665, 1487, 1283  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{15}\text{H}_{12}\text{ClF}_2\text{IN}_2\text{O}_4\text{S}$  C, 34.87/34.98; H, 2.34/2.32; N, 5.42/5.32.

Step b: Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-benzamide

To a suspension comprised of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-dimethylsulfamoyl-benzoic acid (0.5 g,  $9.68 \times 10^{-4}$  mol) and cyclopropylmethoxylamine hydrochloride (0.13 g,  $1.05 \times 10^{-3}$  mol) in a 1:1 v/v mixture of dichloromethane-tetrahydrofuran (10 ml) was added diisopropylethylamine (0.65 ml,  $3.73 \times 10^{-3}$  mol) followed by the addition of solid PyBOP (0.55 g,  $1.06 \times 10^{-3}$  mol). The reaction mixture was stirred at ambient temperature for three days. The mixture was concentrated *in vacuo* to a red oil. The crude product was treated with 10 % aqueous hydrochloric acid (150

ml) and was extracted with diethyl ether (150 ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to a crude solid. The solid was triturated with dichloromethane-hexanes and recovered by vacuum filtration to afford 0.3558 g of the white powder product; 63 % yield; mp 222-225 °C DEC;

5 <sup>1</sup>H-NMR (400 MHz; DMSO) δ 11.97 (s, 1H), 9.32 (s, 1H), 7.60 (d, 1H, J=1.9 Hz), 7.49 (d, 1H, J=5.8 Hz), 7.33 (dd, 1H, J=8.4, 1.9 Hz), 6.70 (dd, 1H, 8.4, 6.3 Hz), 3.43 (d, 2H, J=7.2 Hz), 2.53 (s, 6H), 0.87-0.83 (m, 1H), 0.30-0.25 (m, 2H), 0.03-0.00 (m, 2H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -127.67 (d, J=19.8 Hz), -139.32 (d, J=19.8 Hz); MS (APCI+) 586 (M+1, 100); (APCI-) 584 (M-1, 40),

10 514 (100); IR (KBr) 3263, 1644, 1585, 1507, 1480 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>19</sub>H<sub>19</sub>ClF<sub>2</sub>IN<sub>3</sub>O<sub>4</sub>S C, 38.96/39.08; H, 3.27/3.18; N, 7.17/7.17.

#### EXAMPLE 6C

15 Preparation of N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methyl-phenylamino)-benzamide (PD 252745)

Step a: Preparation of 3,4-difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (PD 224340)

20 Same procedure and same scale as Example 4C, Step a, except 4-iodo-2-methylaniline was used instead of 2-chloro-4-iodoaniline; afforded 0.9592 g of the off-white powder product; 55 % yield; mp 235-238 °C; <sup>1</sup>H-NMR (400 MHz; DMSO) δ 9.69 (s, 1H), 8.04 (d, 1H, J=6.1 Hz), 7.60 (d, 1H, J=1.5 Hz), 7.45 (dd, 1H, J=8.3, 1.7 Hz), 6.88 (dd, 1H, J=8.3, 5.4 Hz), 2.70 (s, 6H),

25 2.21 (s, 3H); <sup>19</sup>F-NMR (376 MHz; DMSO) δ -126.25 (d, J=16.8 Hz), -142.74 (d, J=19.8 Hz); MS (APCI+) 497 (M+1, 69), 357 (70), 316 (100); (APCI-) 495 (M-1, 3), 127 (100); IR (KBr) 3240, 1686, 1512, 1473, 1341, 1151 cm<sup>-1</sup>; Anal. calcd/found for: C<sub>16</sub>H<sub>15</sub>F<sub>2</sub>IN<sub>2</sub>O<sub>4</sub>S C, 38.72/38.70; H, 3.05/3.01; N, 5.64/5.49.

30 Step b: Preparation of N-cyclopropylmethoxy-3,4-difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

Same procedure and same scale as Example 4C, Step b, except the product was purified by recrystallization from absolute ethanol to afford 0.1718 g of the pale yellow microcrystalline product; 28 % yield; mp 171-172 °C; <sup>1</sup>H-

35 NMR (400 MHz; DMSO) δ 11.79 (s, 1H), 8.91 (s, 1H), 7.40 (d, 1H, J=4.3 Hz),



7.36 (s, 1H), 7.21 (d, 1H, J=8.2 Hz), 6.54 (dd, 1H, 8.2, 4.3 Hz), 3.30 (d, 2H, J=6.5 Hz), 2.52 (s, 6H), 2.00 (s, 3H), 0.85-0.75 (m, 1H), 0.29 (d, 2H, J=7.7 Hz), 0.01 (d, 2H, J=4.1 Hz);  $^{19}\text{F}$ -NMR (376 MHz; DMSO)  $\delta$  -128.94 (s), -143.32 (d, J=19.8 Hz); MS (APCI+) 566 (M+1, 100); (APCI-) 564 (M-1, 85), 494 (100); IR (KBr) 1649, 1609, 1588, 1512, 1475  $\text{cm}^{-1}$ ; Anal. calcd/found for:  $\text{C}_{20}\text{H}_{22}\text{F}_2\text{IN}_3\text{O}_4\text{S}$  C, 42.49/42.42; H, 3.92/3.78; N, 7.43/7.40.

## EXAMPLE 7C

10 Preparation of 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-dimethylsulfamoyl-benzamide

Step a: Preparation of 4-methyl-benzene-N,N-dimethylsulfonamide

To a stirring solution comprised of *para*-toluenesulfonyl chloride in dichloromethane at 0 °C is introduced excess gaseous dimethylamine. The precipitate is removed by filtration and the filtrate is concentrated *in vacuo* to obtain the product.

20 Step b: Preparation of 4-methyl-3-nitro-benzene-N,N-dimethylsulfonamide

To a gently stirring solution comprised of 1 molar equivalent of fuming nitric acid in excess concentrated sulfuric acid is added 1 molar equivalent of 4-methyl-benzene-N,N-dimethylsulfonamide in increments. The mixture is stirred for one hour and then poured over chilled water. The mixture is extracted with a suitable solvent like diethyl ether or dichloromethane. The organic phase is dried over a suitable drying agent like magnesium sulfate and concentrated *in vacuo* to afford a crude product which may be purified by normal methods such as chromatography or crystallization from a solvent like chloroform or heptane.

30 Step c: Preparation of 3-amino-4-methyl-benzene-N,N-dimethylsulfonamide

The compound 4-methyl-3-nitro-benzene-N,N-dimethylsulfonamide is dissolved in ethanol. A catalyst like Raney nickel is added and the mixture hydrogenated in a shaker. The catalyst is removed by filtration. The solvent is removed *in vacuo* to give a product which may be purified if necessary by

chromatography or crystallization from an appropriate solvent like chloroform or heptane-ethyl acetate.

Step d: Preparation of 3-fluoro-4-methyl-benzene-N,N-dimethylsulfonamide

The compound 3-amino-4-methyl-benzene-N,N-dimethylsulfonamide is diazotized with an alkyl nitrite like *tert*-butyl nitrite under anhydrous conditions in a non-reactive solvent like tetrahydrofuran or dichloromethane. The intermediate diazonium species is then treated with pyridinium fluoride to give the product, which may be purified by chromatography or crystallization.

Step e: Preparation of 4-dimethylsulfamoyl-2-fluoro-benzoic acid

A mixture comprised of 3-fluoro-4-methyl-benzene-N,N-dimethylsulfonamide and potassium permanganate (2.2 molar equivalents) in water is brought to reflux for four hours. The reaction mixture is filtered through celite. The filtrate is treated with activated carbon and refiltered through fresh celite. The second filtrate is acidified with concentrated hydrochloric acid to pH 0. The mixture is allowed to cool and is extracted with diethyl ether. The organic phase is dried over a drying agent like magnesium sulfate and is concentrated *in vacuo*. The product may be purified by recrystallization from an appropriate solvent like ethanol or chloroform.

Step f: Preparation of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-benzoic acid

To a stirring cold (-78 °C) solution comprised of 2-chloro-4-iodoaniline (1 molar equivalent) in anhydrous tetrahydrofuran under a nitrogen atmosphere is added a commercially available lithium diisopropylamide solution (Aldrich, 2.0 M in tetrahydrofuran/heptane/ethylbenzene, 1 molar equivalent). After stirring for 5 minutes, a solution comprised of 4-dimethylsulfamoyl-2-fluoro-benzoic acid (1 molar equivalent) in tetrahydrofuran is added. The cold bath is removed and the reaction mixture is stirred for 2 hours. The reaction mixture is then partitioned between diethyl ether and dilute aqueous hydrochloric acid. The organic phase is washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to afford

a product which may be purified by chromatography or recrystallization from an appropriate solvent like chloroform or heptane-ethanol.

5      Step g: Preparation of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-benzoic acid O-(tetrahydro-2H-pyran-2-yl)-oxyamide

          A solution comprised of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-benzoic acid, O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (1.25 molar equivalents), benzotriazole-1-yl-oxy-*tris*-pyrrolidino-phosphonium  
10      hexafluorophosphate (1.25 molar equivalents), and diisopropylethylamine (3 molar equivalents) in 1:1 v/v tetrahydrofuran-dichloromethane is stirred for 30 minutes. The reaction mixture is concentrated *in vacuo* and the residue is purified by flash chromatography; elution with dichloromethane affords the desired product. The product may be recrystallized with an appropriate  
15      solvent like methanol if further purification is necessary.

          Step h: Preparation of 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-N-hydroxy-benzamide

          The compound 2-(2-chloro-4-iodo-phenylamino)-4-dimethylsulfamoyl-benzoic acid O-(tetrahydro-2H-pyran-2-yl)-oxyamide is dissolved in an  
20      appropriate hydrogen chloride-saturated solvent like methanol or ethanol. Once homogeneous, the solution is concentrated *in vacuo* to give the desired product. The product may be triturated with an appropriate solvent like chloroform or dichloromethane if further purification is necessary.

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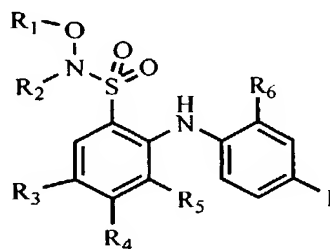
## F. Other Embodiments

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

## CLAIMS

1. A method for treating chronic pain, said method comprising administering to a subject in need of such treatment a composition comprising a MEK inhibitor selected from: a compound of formula (I):



(I)

10  $R_1$  is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub> cycloalkyl)-C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl, (CH<sub>2</sub>)<sub>2-4</sub> OR<sub>C</sub> or (CH<sub>2</sub>)<sub>2-4</sub> NR<sub>C</sub>R<sub>D</sub> ;

15

$R_2$  is H, C<sub>1-4</sub> alkyl, phenyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical, or (C<sub>3-6</sub> cycloalkyl) methyl;

each of  $R_3$  and  $R_4$  is independently selected from H, F, NO<sub>2</sub>, Br and Cl;

20

$R_5$  is selected from H and F;

$R_6$  is H, F, Cl or CH<sub>3</sub>;

25 each of  $R_C$  and  $R_D$  is independently selected from H, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, and phenyl; or NR<sub>C</sub>R<sub>D</sub> may be a piperidino, morpholino, or N-(C<sub>1-6</sub> alkyl)piperazino ring;

wherein each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>; and

- 5 wherein each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2  
10 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxyl, amino, and NO<sub>2</sub>;

or a pharmaceutically acceptable salt or C<sub>1-8</sub> ester thereof.

15

2. The method of claim 1, wherein said chronic pain is selected from neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

3. The method of claim 2, wherein said chronic pain is a type of  
20 neuropathic pain.

4. The method of claim 3, wherein said neuropathic pain is associated with one of the following: inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis,  
25 viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and any other nerve injury between the peripheral nervous system and the central nervous system, inclusively.

5. The method of claim 2, wherein said chronic pain is associated with  
30 chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

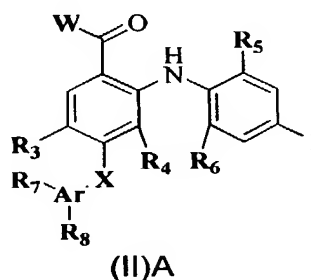
6. The method of claim 2, wherein said chronic pain is associated with idiopathic pain.
- 5 7. The method of claim 1, wherein said chronic pain is associated with inflammation.
8. The method of claim 1, wherein said chronic pain is associated with arthritis.
- 10 9. The method of claim 1, wherein said chronic pain is associated with post-operative pain.
- 15 10. The method of claim 1, wherein  $R_3$  is bromo or chloro.
11. The method of claim 1, wherein  $R_4$  is fluoro.
12. The method of claim 1, wherein  $R_5$  is H.
- 20 13. The method of claim 12, wherein each of  $R_4$  and  $R_5$  is H.
14. The method of claim 1, wherein each of  $R_4$  and  $R_5$  is fluoro.
- 25 15. The method of claim 14, wherein  $R_3$  is bromo.
16. The method of claim 14, wherein  $R_3$  is fluoro.
17. The method of claim 1, wherein  $R_4$  is nitro.
- 30 18. The method of claim 16, wherein  $R_5$  is H.

19. The method of claim 1, wherein  $R_6$  is chloro.
20. The method of claim 1, wherein  $R_6$  is methyl.
- 5 21. The method of claim 1, wherein  $R_1$  is H or  $C_{1-4}$  alkyl, and  $R_2$  is H.
22. The method of claim 1, wherein  $R_1$  is ( $C_{3-6}$  cycloalkyl)methyl.
23. The method of claim 1, wherein  $R_1$  is H.
- 10 24. The method of claim 1, wherein  $R_1$  is  $(CH_2)_{2-4}OR_C$  or  $(CH_2)_{2-4}NR_C R_D$ .
25. The method of claim 1, wherein said MEK inhibitor has a structure selected from: 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 4-fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4,5-trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 5-bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonic acid; N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide; and
- 30 N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide.



26. The method of claim 1, wherein said MEK inhibitor has a structure selected from: 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-4-nitro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzenesulfonamide; and 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzenesulfonamide.

27. A method for treating chronic pain, said method comprising administering to a subject in need of such treatment a composition comprising a MEK inhibitor selected from a compound having the formula (II)A:



W is  $OR_1$ ,  $NR_2OR_1$ ,  $NR_AR_B$ ,  $NR_2NR_AR_B$ , or  $NR_2(CH_2)_{2-4}NR_AR_B$ ;

$R_1$  is H,  $C_{1-8}$  alkyl,  $C_{3-8}$  alkenyl,  $C_{3-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, phenyl, (phenyl) $C_{1-4}$  alkyl, (phenyl) $C_{3-4}$  alkenyl, (phenyl) $C_{3-4}$  alkynyl, ( $C_{3-8}$  cycloalkyl)-

$C_{1-4}$  alkyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$  alkenyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$  alkynyl,  $C_{3-8}$  heterocyclic radical, ( $C_{3-8}$  heterocyclic radical) $C_{1-4}$  alkyl, ( $C_{3-8}$  heterocyclic radical) $C_{3-4}$  alkenyl, ( $C_{3-8}$  heterocyclic radical) $C_{3-4}$  alkynyl or  $(CH_2)_{2-4}NR_AR_B$ ;

$R_2$  is H, phenyl,  $C_{1-4}$  alkyl,  $C_{3-4}$  alkenyl,  $C_{3-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, or ( $C_{3-8}$  cycloalkyl)- $C_{1-4}$  alkyl;

$R_A$  is H,  $C_{1-6}$  alkyl,  $C_{3-8}$  alkenyl,  $C_{3-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, phenyl, ( $C_{3-8}$  cycloalkyl) $C_{1-4}$  alkyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$  alkenyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$

alkynyl,  $C_{3-8}$  heterocyclic radical, ( $C_{3-8}$  heterocyclic radical) $C_{1-4}$  alkyl, (aminosulfonyl)phenyl, [(aminosulfonyl)phenyl] $C_{1-4}$  alkyl, (aminosulfonyl) $C_{1-6}$  alkyl, (aminosulfonyl) $C_{3-6}$  cycloalkyl, or [(aminosulfonyl) $C_{3-6}$  cycloalkyl] $C_{1-4}$  alkyl;

$R_B$  is H,  $C_{1-8}$  alkyl,  $C_{3-8}$  alkenyl,  $C_{3-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, or  $C_{6-8}$  aryl;

$R_3$  is halo,  $NO_2$ ,  $SO_2NR_I(CH_2)_{2-4}NR_ER_F$ ,  $SO_2NR_IR_K$  or  $(CO)T$ ;

T is  $C_{1-8}$  alkyl,  $C_{3-8}$  cycloalkyl,  $(NR_ER_F)C_{1-4}$  alkyl,  $OR_F$ ,  $NR_I(CH_2)_{2-4}NR_ER_F$ , or  $NR_ER_F$ ;

$R_4$  is H or F;

$R_5$  is H, methyl, halo, or  $NO_2$ ;

$R_6$  is H, methyl, halo, or  $NO_2$ ;

Ar is phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

- each of  $R_7$  and  $R_8$  is independently selected from H, halo,  $C_{1-4}$  alkyl,  $SO_2NR_J(CH_2)_{2-4}NR_GR_H$ ,  $(CO)(CH_2)_{2-4}NR_GR_H$ ,  $(CO)NR_J(CH_2)_{2-4}NR_GR_H$ ,  
 5  $(CO)O(CH_2)_{2-4}NR_GR_H$ ,  $SO_2NR_GR_H$ , and  $(CO)NR_GR_H$ ; provided that where Ar is a pyridyl, each of  $R_7$  and  $R_8$  is H;

- each of  $R_C$ ,  $R_D$ ,  $R_E$ ,  $R_F$ ,  $R_G$ , and  $R_H$  is independently selected from H,  $C_{1-4}$  alkyl,  
 10  $C_{3-4}$  alkenyl,  $C_{3-4}$  alkynyl,  $C_{3-6}$  cycloalkyl, and phenyl; each of  $NR_CR_D$ ,  $NR_ER_F$ , and  $NR_GR_H$  can also be independently morpholinyl, piperazinyl, pyrrolidinyl, or piperadinyl;

- each of  $R_I$  and  $R_J$  is independently H, methyl, or ethyl;  
 15

$R_K$  is  $C_{1-4}$  alkyl,  $C_{3-4}$  alkenyl,  $C_{3-4}$  alkynyl,  $C_{3-6}$  cycloalkyl, or phenyl;

X is O, S, or NH; and

- 20 wherein each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo,  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{2-4}$  alkenyl,  $C_{2-4}$  alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and  $NO_2$ , wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2  
 25 substituents independently selected from halo,  $C_{1-2}$  alkyl, hydroxyl, amino, and  $NO_2$ ;

or a pharmaceutically acceptable salt or  $C_{1-7}$  ester thereof.

28. The method of claim 27, wherein said chronic pain is selected from neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

5 29. The method of claim 28, wherein said chronic pain is a type of neuropathic pain.

30. The method of claim 29, wherein said neuropathic pain is associated with one of the following: inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma,  
10 vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and any other nerve injury between the peripheral nervous system and the central nervous system, inclusively.

15 31. The method of claim 28, wherein said chronic pain is associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

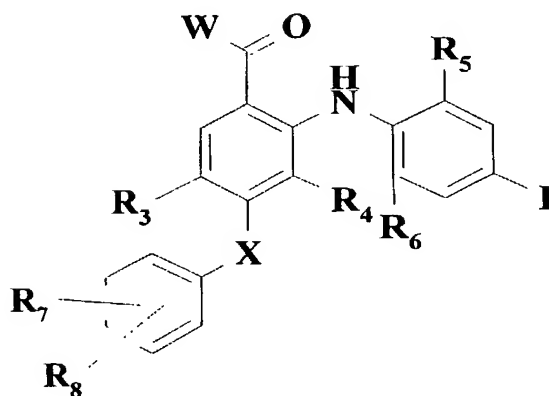
32. The method of claim 28, wherein said chronic pain is associated with idiopathic pain.  
20

33. The method of claim 27, wherein said chronic pain is associated with inflammation.

34. The method of claim 27, wherein said chronic pain is associated with arthritis.  
25

35. The method of claim 27, wherein said chronic pain is associated with post-operative pain.

36. A method of claim 27, having the following formula (I)A:



(I)A

5 wherein

W is  $OR_1$ ,  $NR_2OR_1$ ,  $NR_AR_B$ ,  $NR_2NR_AR_B$ , or  $NR_2(CH_2)_{2-4}NR_AR_B$ ;

$R_1$  is H,  $C_{1-8}$  alkyl,  $C_{3-8}$  alkenyl,  $C_{3-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, phenyl,  
 10 (phenyl) $C_{1-4}$  alkyl, (phenyl) $C_{3-4}$  alkenyl, (phenyl) $C_{3-4}$  alkynyl, ( $C_{3-8}$   
 cycloalkyl)-  
 $C_{1-4}$  alkyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$  alkenyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$  alkynyl,  $C_{3-8}$   
 heterocyclic radical, ( $C_{3-8}$  heterocyclic radical) $C_{1-4}$  alkyl, ( $C_{3-8}$  heterocyclic  
 radical) $C_{3-4}$  alkenyl, ( $C_{3-8}$  heterocyclic radical) $C_{3-4}$  alkynyl or  $(CH_2)_{2-4}NR_AR_B$ ;

15

$R_2$  is H, phenyl,  $C_{1-4}$  alkyl,  $C_{3-4}$  alkenyl,  $C_{3-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, or  
 ( $C_{3-8}$  cycloalkyl)- $C_{1-4}$  alkyl;

$R_A$  is H,  $C_{1-6}$  alkyl,  $C_{3-8}$  alkenyl,  $C_{3-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, phenyl, ( $C_{3-8}$   
 cycloalkyl) $C_{1-4}$  alkyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$  alkenyl, ( $C_{3-8}$  cycloalkyl) $C_{3-4}$   
 20 alkynyl,  $C_{3-8}$  heterocyclic radical, ( $C_{3-8}$  heterocyclic radical) $C_{1-4}$  alkyl,  
 (aminosulfonyl)phenyl, [(aminosulfonyl)phenyl] $C_{1-4}$  alkyl, (aminosulfonyl) $C_{1-6}$

alkyl, (aminosulfonyl)C<sub>3-6</sub> cycloalkyl, or [(aminosulfonyl)C<sub>3-6</sub> cycloalkyl]C<sub>1-4</sub> alkyl;

R<sub>B</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or C<sub>6-8</sub> aryl;

R<sub>3</sub> is halo, NO<sub>2</sub>, SO<sub>2</sub>NR<sub>I</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>E</sub>R<sub>F</sub>, SO<sub>2</sub>NR<sub>I</sub>R<sub>K</sub> or (CO)T;

T is C<sub>1-8</sub> alkyl, C<sub>3-8</sub> cycloalkyl, (NR<sub>E</sub>R<sub>F</sub>)C<sub>1-4</sub> alkyl, OR<sub>F</sub>, NR<sub>I</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>E</sub>R<sub>F</sub>, or NR<sub>E</sub>R<sub>F</sub>;

R<sub>4</sub> is H or F;

R<sub>5</sub> is H, methyl, halo, or NO<sub>2</sub>;

R<sub>6</sub> is H, methyl, halo, or NO<sub>2</sub>;

each of R<sub>7</sub> and R<sub>8</sub> is independently selected from H, halo, C<sub>1-4</sub> alkyl, SO<sub>2</sub>NR<sub>J</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, (CO)(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, (CO)NR<sub>J</sub>(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, (CO)O(CH<sub>2</sub>)<sub>2-4</sub>NR<sub>G</sub>R<sub>H</sub>, SO<sub>2</sub>NR<sub>G</sub>R<sub>H</sub>, and (CO)NR<sub>G</sub>R<sub>H</sub>;

each of R<sub>C</sub>, R<sub>D</sub>, R<sub>E</sub>, R<sub>F</sub>, R<sub>G</sub>, and R<sub>H</sub> is independently selected from H, C<sub>1-4</sub> alkyl,

C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, and phenyl; each of NR<sub>C</sub>R<sub>D</sub>, NR<sub>E</sub>R<sub>F</sub>, and NR<sub>G</sub>R<sub>H</sub> can also be independently morpholinyl, piperazinyl, pyrrolidinyl, or piperadinyll;

each of R<sub>I</sub> and R<sub>J</sub> is independently H, methyl, or ethyl;

R<sub>K</sub> is C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, or phenyl;

X is O, S, or NH; and

wherein each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxyl, amino, and NO<sub>2</sub>;

or a pharmaceutically acceptable salt or C<sub>1-7</sub> ester thereof.

10

37. A method of claim 27, wherein R<sub>3</sub> is NO<sub>2</sub>.

38. A method of claim 27, wherein R<sub>4</sub> is fluoro.

15

39. A method of claim 27, wherein each of R<sub>3</sub> and R<sub>4</sub> is independently selected from H and fluoro.

40. A method of claim 27, wherein R<sub>5</sub> is methyl, fluoro, or chloro.

20

41. A method of claim 27, wherein R<sub>6</sub> is methyl, chloro, fluoro, nitro, or hydrogen.

42. A method of claim 41, wherein R<sub>6</sub> is H.

25

43. A method of claim 41, wherein R<sub>6</sub> is fluoro.

44. A method of claim 27, wherein R<sub>K</sub> is methyl or ethyl.

30

45. A method of claim 27, wherein R<sub>1</sub> is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenyl, phenethyl, allyl, C<sub>2-5</sub> alkenyl, C<sub>3-6</sub> cycloalkyl, (C<sub>3-5</sub> cycloalkyl)C<sub>1-2</sub> alkyl, (C<sub>3-5</sub> heterocyclic radical)C<sub>1-2</sub> alkyl, or (CH<sub>2</sub>)<sub>2-4</sub> NR<sub>C</sub>R<sub>D</sub>.

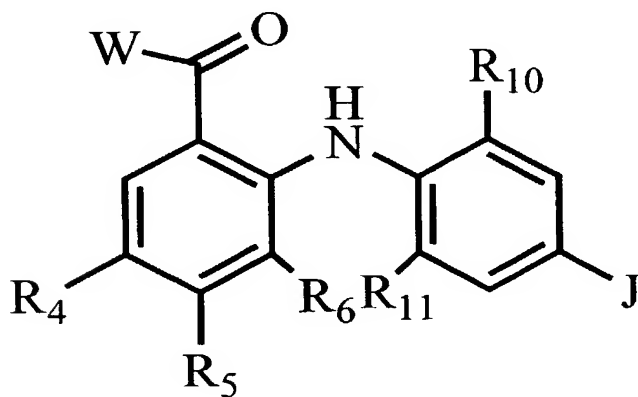
46. A method of claim 45, wherein  $R_1$  is H or (C<sub>3-4</sub> cycloalkyl)-C<sub>1-2</sub> alkyl.
- 5 47. A method of claim 27, wherein  $R_2$  is H or methyl.
48. A method of claim 27, wherein  $R_A$  has at least one hydroxyl substituent.
- 10 49. A method of claim 27, wherein  $R_A$  is H, methyl, ethyl, isobutyl, hydroxyethyl, phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxy-propyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and  $R_B$  is H; or where  $R_B$  is methyl and  $R_A$  is phenyl.
- 15 50. A method of claim 27, wherein W is  $NR_AR_B$  or  $NR_2NR_AR_B$ .
51. A method of claim 27, wherein W is  $NR_2(CH_2)_{2-4}NR_AR_B$  or  $O(CH_2)_{2-3}NR_AR_B$ .
- 20 52. A method of claim 27, wherein W is  $NR_2OR_1$ .
53. A method of claim 27, wherein W is  $OR_B$ .
54. A method of claim 27, wherein  $R_7$  is in the para position relative  
25 to X.
55. A method of claim 54, wherein  $R_7$  is iodo.
56. A method of claim 27, wherein  $R_8$  is in the ortho position relative  
30 to X.



57. A method of claim 27 having the formula 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

58. A method of claim 27, wherein said MEK inhibitor has a structure selected from: 2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-(4-sulfamoyl-phenylamino)-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-phenylamino-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-phenoxy-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-phenylsulfanyl-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3-fluoro-4-(methyl-phenyl-amino)-5-nitro-benzoic acid; benzamide, 2-[(2-chloro-4-iodophenyl)amino]-3-fluoro-N-hydroxy-4-[[4-[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-5-nitro-; benzamide, 2-[(2-chloro-4-iodophenyl)amino]-4-[[4-[(dimethylamino)carbonyl]phenyl]amino]-3-fluoro-N-hydroxy-5-nitro-; 2-(2-chloro-4-iodo-phenylamino)-3,5-difluoro-4-phenylamino-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-(3-sulfamoyl-phenylamino)-benzoic acid; and 2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-4-(2-sulfamoyl-phenylamino)-benzoic acid; and the corresponding hydroxamic acids and cyclopropylmethyl hydroxamates.

59. A method for treating chronic pain, said method comprising administering to a subject in need of such treatment a composition comprising a MEK inhibitor selected from a compound of formula (I)B:



(I)B

wherein

- 5 W is  $OR_1$ ,  $NR_2OR_1$ ,  $NR_AR_B$ ,  $NR_2NR_AR_B$ ,  $O(CH_2)_{1-4}NR_AR_B$ , or  $NR_2(CH_2)_{1-4}NR_AR_B$ ;  
 $O(CH_2)_{1-4}OR_1$ , or  $NR_2(CH_2)_{1-4}OR_1$ ;

- 10  $R_1$  is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub> cycloalkyl)-  
 C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, or (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl;

- 15 each of  $R_2$  and  $R_3$  is independently H, phenyl, C<sub>1-4</sub> alkyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl;

- each of  $R_4$ ,  $R_5$  and  $R_6$  is independently H, Cl, F, or Br;

- 20  $R_A$  is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (aminosulfonyl)phenyl, [(aminosulfonyl)phenyl]C<sub>1-4</sub> alkyl, (aminosulfonyl)C<sub>1-6</sub>  
 25 alkyl, (aminosulfonyl)C<sub>3-6</sub> cycloalkyl, or [(aminosulfonyl)C<sub>3-6</sub> cycloalkyl]C<sub>1-4</sub> alkyl;

$R_B$  is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or phenyl;

- 30 J is  $SR_C$ ,  $OR_C$ ,  $SO_2R_C$ ,  $SOR_C$ ,  $SO_2NR_DRE$ , C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>5-8</sub> cycloalkenyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl,

(C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, -M'E'G', (heterocyclic radical)-M'-E'-G', or (cycloalkyl)-M'-E'-G';

5 M' is O, SO, SO<sub>2</sub>, NR<sub>E</sub>, (CO)NR<sub>E</sub>, NR<sub>E</sub>(CO), SO<sub>2</sub>NR<sub>E</sub>, NR<sub>E</sub>SO<sub>2</sub>, or CH<sub>2</sub>;

E' is absent (a covalent bond), (CH<sub>2</sub>)<sub>1-4</sub> or (CH<sub>2</sub>)<sub>m</sub>O(CH<sub>2</sub>)<sub>p</sub> where 1 ≤ (each of m and p independently) ≤ 3 and 2 ≤ (m + p) ≤ 4;

10

G' is OR<sub>3</sub>, SO<sub>2</sub>R<sub>C</sub>, or NR<sub>F</sub>R<sub>G</sub>; provided that where p = 1, then G' is H;

each of R<sub>C</sub>, R<sub>D</sub>, R<sub>E</sub>, R<sub>F</sub> and R<sub>G</sub> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical,  
 15 and phenyl; NR<sub>F</sub>R<sub>G</sub> and NR<sub>D</sub>R<sub>E</sub> can each also independently be selected from morpholinyl, pyrazinyl, piperazinyl, pyrrolidinyl, or piperadinyl;

R<sub>10</sub> is H, C<sub>1-4</sub> alkyl, halo, NO<sub>2</sub>, or SO<sub>2</sub>NR<sub>H</sub>R<sub>i</sub>; and

20 R<sub>11</sub> is H, halo, or NO<sub>2</sub>;

wherein each hydrocarbon radical or heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, phenyl, hydroxy,  
 25 amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxy, amino, and NO<sub>2</sub>;

30 or a pharmaceutically acceptable salt or C<sub>1-7</sub> ester thereof.

60. The method of claim 59, wherein said chronic pain is selected from neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

5 61. The method of claim 60, wherein said chronic pain is a type of neuropathic pain.

62. The method of claim 61, wherein said neuropathic pain is associated with one of the following: inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma,  
10 vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and any other nerve injury between the peripheral nervous system and the central nervous system, inclusively.

15 63. The method of claim 60, wherein said chronic pain is associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

64. The method of claim 60, wherein said chronic pain is associated with idiopathic pain.

20

65. The method of claim 59, wherein said chronic pain is associated with inflammation.

66. The method of claim 59, wherein said chronic pain is associated  
25 with arthritis.

67. The method of claim 59, wherein said chronic pain is associated with post-operative pain.

30 68. A method of claim 59, wherein  $R_C$  is  $C_{1-2}$  alkyl.

69. A method of claim 59, wherein W is OH.
70. A method of claim 59, wherein W is NHOH.
- 5 71. A method of claim 59, wherein W is NHO(cyclopropylmethyl).
72. A method of claim 59, wherein R<sub>10</sub> is methyl or chloro.
- 10 73. A method of claim 59, where R<sub>11</sub> is fluoro.
74. A method of claim 59, where R<sub>11</sub> is H.
75. A method of claim 59, wherein J is trihalomethyl or methylthio.
- 15 76. A method of claim 59, wherein J is 1,2,5-thiadiazol-3-yl.
77. A method of claim 59, wherein J is SO<sub>2</sub>CH<sub>3</sub>.
- 20 78. A method of claim 59, wherein J is SOCH<sub>3</sub>.
79. A method of claim 59, wherein J is C<sub>2-8</sub> alkynyl where the triple bond is between the carbon atoms alpha and beta to the phenyl group.
- 25 80. A method of claim 59, wherein R<sub>1</sub> has at least one hydroxy substituent.
81. A method of claim 59, wherein R<sub>1</sub> is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenethyl, allyl, C<sub>3-5</sub> alkenyl, C<sub>3-5</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, (C<sub>3-5</sub> cycloalkyl)C<sub>1-2</sub> alkyl, or (C<sub>3-5</sub> heterocyclic radical)-C<sub>1-2</sub> alkyl.
- 30

82. A method of claim 59, wherein  $R_1$  is H or (C<sub>3-4</sub> cycloalkyl)-C<sub>1-2</sub> alkyl.
83. A method of claim 59, wherein  $R_2$  is H, methyl, C<sub>3-4</sub> alkynyl, C<sub>3-5</sub> cycloalkyl, or (C<sub>3-5</sub> cycloalkyl)methyl.
84. A method of claim 59, wherein  $R_A$  is H, methyl, ethyl, isobutyl, hydroxyethyl, hydroxypropyl, cyclopropylmethyl, cyclobutylmethyl, C<sub>2-4</sub> alkynyl, phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxy-propyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and  $R_B$  is H; or where  $R_B$  is methyl and  $R_A$  is phenyl.
85. A method of claim 59, wherein each of  $R_4$  and  $R_6$  is H, and  $R_5$  is F.
86. A method of claim 59, wherein each of  $R_4$ ,  $R_5$ , and  $R_6$  is F.
87. A method of claim 59, wherein each of  $R_4$  and  $R_5$  is F and  $R_6$  is Br.
88. A method of claim 59, wherein  $R_5$  is F.
89. A method of claim 59, wherein said MEK inhibitor has a structure selected from: 4-fluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 2-(4-methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzoic acid; 3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzoic acid;

3,4,5-trifluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzoic acid; 4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 5-bromo-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzoic acid; 3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzoic acid; 2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzoic acid; N-cyclopropylmethoxy-4-fluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-cyclopropylmethoxy-4-fluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; and N-cyclopropylmethoxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzamide.

90. A method of claim 59, wherein said MEK inhibitor has a structure selected from: 4-fluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; 5-bromo-3,4-difluoro-N-hydroxy-2-(2-methyl-4-

methylsulfanyl-phenylamino)-benzamide; 3,4-difluoro-N-hydroxy-2-(4-  
 methanesulfinyl-2-methyl-phenylamino)-benzamide; N-hydroxy-2-(4-  
 methanesulfinyl-2-methyl-phenylamino)-4-nitro-benzamide; 3,4,5-trifluoro-N-  
 hydroxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; 3,4-  
 5 difluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-benzamide; N-  
 hydroxy-2-(2-methyl-4-methylsulfanyl-phenylamino)-4-nitro-benzamide; 8:  
 3,4,5-trifluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-  
 benzamide; 4-fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-  
 benzamide; 5-bromo-3,4-difluoro-N-hydroxy-2-(4-methanesulfonyl-2-methyl-  
 10 phenylamino)-benzamide; 3,4,5-trifluoro-N-hydroxy-2-(2-methyl-4-  
 methylsulfanyl-phenylamino)-benzamide; 4-fluoro-N-hydroxy-2-(4-  
 methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-bromo-3,4-difluoro-N-  
 hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 3,4-difluoro-  
 N-hydroxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-benzamide; and N-  
 15 hydroxy-2-(4-methanesulfonyl-2-methyl-phenylamino)-4-nitro-benzamide.

91. A method of claim 59, wherein said MEK inhibitor has a  
 structure selected from: 3,4-difluoro-2-(4-imidazol-1-yl-2-methyl-  
 phenylamino)-benzoic acid; N-cyclopropylmethoxy-3,4-difluoro-2-(4-imidazol-  
 20 1-yl-2-methyl-phenylamino)-benzamide; 3,4-difluoro-N-hydroxy-2-(4-imidazol-  
 1-yl-2-methyl-phenylamino)-benzamide; 3,4,5-trifluoro-2-(2-methyl-4-  
 [1,2,5]thiadiazol-3-yl-phenylamino)-benzoic acid; N-cyclopropylmethoxy-3,4,5-  
 trifluoro-2-(2-methyl-4-[1,2,5]thiadiazol-3-yl-phenylamino)-benzamide; 3,4,5-  
 trifluoro-N-hydroxy-2-(2-methyl-4-[1,2,5]thiadiazol-3-yl-phenylamino)-  
 25 benzamide; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-3,4,5-  
 trifluoro-benzoic acid; 2-[4-(4-chloro-[1,2,5]thiadiazol-3-yl)-2-methyl-  
 phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-[4-(4-chloro-  
 [1,2,5]thiadiazol-3-yl)-2-methyl-phenylamino]-3,4,5-trifluoro-N-hydroxy-  
 benzamide; 2-[4-[4-(2-dimethylamino-ethoxy)-[1,2,5]thiadiazol-3-yl]-2-methyl-  
 30 phenylamino]-3,4,5-trifluoro-benzoic acid; N-cyclopropylmethoxy-3,4,5-  
 trifluoro-2-[2-methyl-4-[4-(2-piperidin-1-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-



phenylamino}-benzamide; and 3,4,5-trifluoro-N-hydroxy-2-{2-methyl-4-[4-(2-morpholin-4-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino}-benzamide.

92. The method of claim 59, wherein said MEK inhibitor has a
- 5 structure selected from: 5-bromo-2-(2-chloro-4-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-chloro-4-methanesulfinyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 2-(2-chloro-methylsulfanyl-phenylamino)-3,4-difluoro-benzoic acid; 5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-3,4-
- 10 difluoro-benzoic acid; 2-(2-Chloro-4-methanesulfonyl-phenylamino)-3,4-difluoro-benzoic acid; 5-bromo-2-(2-chloro-4-methylsulfanyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfinyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methanesulfonyl-phenylamino)- N-cyclopropylmethoxy-3,4,5-trifluoro-
- 15 benzamide; 2-(2-chloro-4-methylsulfanyl-phenylamino)- N-cyclopropylmethoxy-3,4-difluoro-benzamide;
- 2-(2-chloro-4-methanesulfinyl-phenylamino)- N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 5-bromo-2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-methylsulfanyl-
- 20 phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-chloro-4-methanesulfonyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;
- 2-[2-chloro 4-(3H-imidazol-1-yl)-phenylamino]-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-[1,2,5]thiadiazol-3-yl-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-[4-(2-chloro-4-chloro-
- 25 [1,2,5]thiadiazol-3-yl)-phenylamino]-3,4,5-trifluoro-benzoic acid; 2-[2-chloro-4-(4-chloro-[1,2,5]thiadiazol-3-yl)-phenylamino]-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-{4-[4-(2-dimethylamino-ethoxy)-[1,2,5]thiadiazol-3-yl]-2-methyl-phenylamino}-3,4,5-trifluoro-benzoic acid; and 2-{2-chloro-4-[4-(2-piperidin-1-yl-ethoxy)-[1,2,5]thiadiazol-3-yl]-phenylamino}-N-
- 30 cyclopropylmethoxy-3,4,5-trifluoro-benzamide.

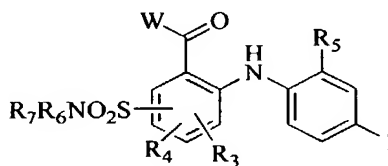
93. The method of claim 59, wherein said MEK inhibitor has a structure selected from: 2-(4-Ethynyl-2-methyl-phenylamino)-4-fluoro-benzoic acid; 5-Bromo-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-  
 5 benzamide; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-4-nitro-Benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(4-Ethynyl-2-methyl-phenylamino)-4-nitro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-  
 10 benzamide; 4-Fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-phenylamino)-benzamide; 5-Bromo-2-(4-ethynyl-2-methyl-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4,5-trifluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-4-fluoro-benzamide; 5-Bromo-N-cyclopropylmethoxy-2-(4-ethynyl-2-methyl-  
 15 phenylamino)-3,4-difluoro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-N-hydroxy-4-nitro-benzamide; 2-(4-Ethynyl-2-methyl-phenylamino)-4-fluoro-benzoic acid; N-Cyclopropylmethoxy-2-(4-ethynyl-2-methyl-phenylamino)-4-fluoro-benzamide; and 4-Fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methyl-  
 20 phenylamino)-benzamide.

94. The method of claim 59, wherein said MEK inhibitor has a structure selected from: 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 5-Bromo-2-(2-chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid;  
 25 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-nitro-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)- N-hydroxy-3,4,5-trifluoro- benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-3,4-difluoro-benzoic acid; 2-(4-Ethynyl-2-chloro-phenylamino)-4-nitro-benzoic acid; 2-(2-Chloro-4-ethynyl-phenylamino)- N-Cyclopropylmethoxy-3,4,5-trifluoro-benzamide; 2-(2-  
 30 chloro-4-methanesulfinyl-phenylamino)- 4-fluoro-N-hydroxy-benzamide; 5-Bromo-2-(4-ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-3,4,5-trifluoro-benzoic acid; 2-(2-Chloro-

4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-fluoro-benzamide; 5-Bromo-  
 2-(2-chloro-4-ethynyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-  
 benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-3,4-difluoro-N-hydroxy-  
 benzamide; 2-(4-Ethynyl-2-chloro-phenylamino)-N-hydroxy-4-nitro-  
 5 benzamide; 2-(2-Chloro-4-ethynyl-phenylamino)-4-fluoro-benzoic acid; 2-(2-  
 Chloro-4-ethynyl-phenylamino)- N-cyclopropylmethoxy-4-fluoro-benzamide; 2-  
 (2-Chloro-4-methanesulfinyl-phenylamino)- 4-fluoro-N-hydroxy-benzamide;  
 and 2-(2-chloro-4-imidazol-1-yl-phenylamino)- 3,4-Difluoro-benzoic acid.

10 95. A method for treating chronic pain, said method comprising  
 administering to a subject in need of such treatment a composition comprising  
 a MEK inhibitor selected from a compound of formula (I)C:

15



(I)C

20

25 wherein

W is OR<sub>1</sub>, NR<sub>2</sub>OR<sub>1</sub>, NR<sub>A</sub>R<sub>B</sub>, NR<sub>2</sub>NR<sub>A</sub>R<sub>B</sub>, or NR<sub>2</sub>(CH<sub>2</sub>)<sub>2-4</sub> NR<sub>A</sub>R<sub>B</sub>;

R<sub>1</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl,  
 30 (phenyl)C<sub>1-4</sub> alkyl, (phenyl)C<sub>3-4</sub> alkenyl, (phenyl)C<sub>3-4</sub> alkynyl, (C<sub>3-8</sub>  
 cycloalkyl)-

C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> heterocyclic radical)C<sub>3-4</sub> alkynyl or (CH<sub>2</sub>)<sub>2-4</sub>NR<sub>A</sub>R<sub>B</sub>;

- 5 R<sub>2</sub> is H, phenyl, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or (C<sub>3-8</sub> cycloalkyl)-C<sub>1-4</sub> alkyl;

- R<sub>A</sub> is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, phenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>1-4</sub> alkyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkenyl, (C<sub>3-8</sub> cycloalkyl)C<sub>3-4</sub> alkynyl, C<sub>3-8</sub> heterocyclic radical, (C<sub>3-8</sub> heterocyclic radical)C<sub>1-4</sub> alkyl,  
 10 (aminosulfonyl)phenyl, [(aminosulfonyl)phenyl]C<sub>1-4</sub> alkyl, (aminosulfonyl)C<sub>1-6</sub> alkyl, (aminosulfonyl)C<sub>3-6</sub> cycloalkyl, or [(aminosulfonyl)C<sub>3-6</sub> cycloalkyl]C<sub>1-4</sub> alkyl;

- 15 R<sub>B</sub> is H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> alkenyl, C<sub>3-8</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, or C<sub>6-8</sub> aryl;

R<sub>3</sub> is H, F, Cl, Br, or NO<sub>2</sub>;

R<sub>4</sub> is H or F;

20

R<sub>5</sub> is H, methyl or Cl;

- R<sub>6</sub> is H, C<sub>1-4</sub> alkyl, hydroxyethyl, hydroxypropyl, (CH<sub>2</sub>)<sub>2-4</sub>(NR<sub>C</sub>R<sub>D</sub>), phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl or CH<sub>2</sub>Ar, where Ar is phenyl, 2-pyridyl, 3-pyridyl,  
 25 or 4-pyridyl;

- R<sub>7</sub> is H, C<sub>1-4</sub> alkyl, hydroxyethyl, hydroxypropyl, (CH<sub>2</sub>)<sub>2-4</sub>(NR<sub>C</sub>R<sub>D</sub>), phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, or CH<sub>2</sub>Ar, where Ar is phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

30

each of R<sub>C</sub> and R<sub>D</sub> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-4</sub> alkenyl,

C<sub>3-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> heterocyclic radical, and phenyl; NR<sub>C</sub>R<sub>D</sub> can also be selected from morpholinyl, piperazinyl, pyrrolidinyl, or piperadinyl;

wherein each hydrocarbon radical or heterocyclic radical above is  
5 optionally substituted with between 1 and 3 substituents independently  
selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl,  
phenyl, hydroxy, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent  
alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with  
between 1 and 3 substituents independently selected from halo, C<sub>1-2</sub> alkyl,  
10 hydroxy, amino, and NO<sub>2</sub>;

or a pharmaceutically-acceptable salt or C<sub>1-6</sub> ester thereof.

96. The method of claim 95, wherein said chronic pain is selected  
15 from neuropathic pain, idiopathic pain, and pain associated with chronic  
alcoholism, vitamin deficiency, uremia, or hypothyroidism.

97. The method of claim 96, wherein said chronic pain is a type of  
neuropathic pain.

98. The method of claim 97, wherein said neuropathic pain is  
20 associated with one of the following: inflammation, postoperative pain,  
phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and  
postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma,  
vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb  
amputation, post-operative pain, arthritis pain, and any other nerve injury  
25 between the peripheral nervous system and the central nervous system,  
inclusively.

99. The method of claim 96, wherein said chronic pain is associated  
with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

30

100. The method of claim 96, wherein said chronic pain is associated with idiopathic pain.

5 101. The method of claim 95, wherein said chronic pain is associated with inflammation.

102. The method of claim 95, wherein said chronic pain is associated with arthritis.

10 103. The method of claim 95, wherein said chronic pain is associated with post-operative pain.

15 104. A method of claim 95, wherein the sulfamoyl group is *meta* to W(CO)- and *para* to the bridging NH.

105. A method of claim 95, wherein the sulfamoyl group is *para* to W (CO)- and *meta* to the bridging NH.

20 106. A method of claim 95, wherein R<sub>4</sub> is fluoro.

107. A method of claim 95, where R<sub>3</sub> is fluoro.

108. A method of claim 95, where R<sub>3</sub> is H.

25 109. A method of claim 95, wherein W is OH.

110. A method of claim 95, wherein W is NR<sub>2</sub>OR<sub>1</sub>.

30 111. A method of claim 109, wherein each of R<sub>3</sub> and R<sub>4</sub> is fluoro.

112. A method of claim 95, wherein R<sub>1</sub> has at least one hydroxy substituent.

113. A method of claim 95, wherein  $R_1$  is H, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, phenethyl, allyl,  $C_{3-5}$  alkenyl,  $C_{3-5}$  alkynyl,  $C_{3-6}$  cycloalkyl,  $(C_{3-5}$  cycloalkyl) $C_{1-2}$  alkyl, or  $(C_{3-5}$  heterocyclic radical)-  
5  $C_{1-2}$  alkyl.
114. A method of claim 113, wherein  $R_1$  is H or  $(C_{3-4}$  cycloalkyl)-  
 $C_{1-2}$  alkyl.
- 10 115. A method of claim 95, wherein  $R_2$  is H, methyl,  $C_{3-4}$  alkynyl,  $C_{3-5}$  cycloalkyl, or  $(C_{3-5}$  cycloalkyl)methyl.
116. A method of claim 95, wherein  $R_A$  is H, methyl, ethyl, isobutyl, hydroxyethyl, hydroxypropyl, cyclopropylmethyl, cyclobutylmethyl,  $C_{3-4}$   
15 alkynyl, phenyl, 2-piperidin-1-yl-ethyl, 2,3-dihydroxy-propyl, 3-[4-(2-hydroxyethyl)-piperazin-1-yl]-propyl, 2-pyrrolidin-1-yl-ethyl, or 2-diethylamino-ethyl; and  $R_B$  is H; or where  $R_B$  is methyl and  $R_A$  is phenyl.
117. A method of claim 95, wherein  $R_7$  is  $(CH_2)_{2-4}(NR_C R_D)$ .
- 20 118. A method of claim 95, wherein  $NR_C R_D$  is selected from morpholinyl, piperazinyl, pyrrolidinyl, or piperadinyl.
119. A method of claim 95, wherein  $R_5$  is methyl or chloro.
- 25 120. A method of claim 95, wherein said MEK inhibitor has a structure selected from: 2-(2-chloro-4-iodo-phenylamino)-4-sulfamoyl-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-sulfamoyl-benzamide;  
30 2-(2-chloro-4-iodo-phenylamino)-4-(2-morpholin-4-yl-ethylsulfamoyl)-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-

- cyclopropylmethoxy-4-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-sulfamoyl-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-5-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-
- 5 benzamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(2-morpholin-4-yl-ethylsulfamoyl)-benzoic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-5-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(2-morpholin-4-yl-ethylsulfamoyl)-benzamide; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-
- 10 (4-iodo-phenylamino)-benzoic acid; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; N-
- 15 cyclopropylmethoxy-5-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-5-(ethyl-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-
- 20 cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-phenylamino)-benzoic acid; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-pyridin-2-ylmethyl-sulfamoyl)-benzamide; N-
- 25 cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-[(pyridin-2-ylmethyl)-sulfamoyl]-benzamide; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-
- 30 cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-[(pyridin-



3-ylmethyl)-sulfamoyl]-benzamide; N-cyclopropylmethoxy-5-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-5-(ethyl-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(methyl-pyridin-2-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-[(pyridin-2-ylmethyl)-sulfamoyl]-benzamide; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid; 5-(bis-pyridin-3-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-5-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-3-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-5-(ethyl-pyridin-3-ylmethyl-sulfamoyl)-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-3-ylmethyl-sulfamoyl]-benzamide; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid; 5-(bis-pyridin-2-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-pyridin-2-ylmethyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-

cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-2-ylmethyl)-sulfamoyl]-benzamide;  
N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-2-ylmethyl-  
sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-  
difluoro-5-[(2-hydroxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-2-(4-iodo-  
5 phenylamino)-benzamide; 5-(benzyl-pyridin-2-ylmethyl-sulfamoyl)-N-  
cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-  
cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-[(pyridin-4-  
ylmethyl)-sulfamoyl]-benzamide; N-cyclopropylmethoxy-5-(ethyl-pyridin-4-  
ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-iodo-phenylamino)-benzamide; N-  
10 cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-pyridin-4-  
ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-  
hydroxy-propyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-  
benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-4-  
ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-  
15 cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-phenylamino)-5-(methyl-phenyl-  
sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-  
phenylamino)-5-phenylsulfamoyl-benzamide; N-cyclopropylmethoxy-3,4-  
difluoro-2-(4-iodo-phenylamino)-5-(pyridin-3-ylsulfamoyl)-benzamide; N-  
cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-2-ylmethyl-  
20 sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-  
cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-2-ylmethyl-  
sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; 5-(benzyl-pyridin-2-  
ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-  
phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-  
25 methyl-phenylamino)-5-[(pyridin-4-ylmethyl)-sulfamoyl]-benzamide; N-  
cyclopropylmethoxy-5-(ethyl-pyridin-4-ylmethyl-sulfamoyl)-3,4-difluoro-2-(4-  
iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-  
(4-iodo-2-methyl-phenylamino)-5-(methyl-pyridin-4-ylmethyl-sulfamoyl)-  
benzamide; N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-  
30 4-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-  
cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-  
sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-

cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(methyl-phenyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-phenylsulfamoyl-benzamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-5-(pyridin-3-ylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-2-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-benzamide; 5-(benzyl-pyridin-2-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-4-ylmethyl)-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-5-(ethyl-pyridin-4-ylmethyl-sulfamoyl)-3,4-difluoro-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-pyridin-4-ylmethyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxy-propyl)-pyridin-4-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(methyl-phenyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-phenylsulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(pyridin-3-ylsulfamoyl)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-phenylsulfamoyl-benzamide; N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-(pyridin-3-ylsulfamoyl)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 4-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-4-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-phenylamino)-4-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-4-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-

methyl-phenylamino)-4-phenylsulfamoyl-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-(pyridin-3-ylsulfamoyl)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 4-(bis-pyridin-3-ylmethyl-sulfamoyl)-N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-4-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; N-cyclopropylmethoxy-4-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-2-(4-iodo-2-methyl-phenylamino)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-phenylsulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-(pyridin-3-ylsulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-[(pyridin-3-ylmethyl)-sulfamoyl]-benzamide; 4-(bis-pyridin-3-ylmethyl-sulfamoyl)-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-[(2-hydroxy-ethyl)-pyridin-4-ylmethyl-sulfamoyl]-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-(methyl-pyridin-3-ylmethyl-sulfamoyl)-benzamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-[(3-diethylamino-propyl)-pyridin-3-ylmethyl-sulfamoyl]-benzamide; and 5-[bis-(4-methoxy-benzyl)-sulfamoyl]-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid; and 2-(2-chloro-4-iodo-phenylamino)-5-dimethylsulfamoyl-3,4-difluoro-benzoic acid methyl ester.

121. The method of claim 95, wherein said MEK inhibitor has a structure selected from: PD 298458, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(4-methyl-piperazine-1-sulfonyl)-benzamide; PD 298459, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(methyl-phenyl-sulfamoyl)-benzamide; PD 298460, 5-(Allyl-methyl-sulfamoyl)-N-allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzamide; PD 298463, 1-[5-Allyloxycarbamoyl-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonyl]-piperidine-3-carboxylic acid amide; PD 298464, N-Allyloxy-

2-(2-chloro-4-iodo-phenylamino)-5-[(3-dimethylamino-propyl)-methyl-sulfamoyl]-3,4-difluoro-benzamide; PD 298465, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-benzamide; and PD 298467, N-Allyloxy-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-5-(methoxy-methyl-sulfamoyl)-benzamide.

122. The method of claim 1, wherein said MEK inhibitor has a structure selected from: 2-(2-chloro-4-iodo-phenylamino)-*N*-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; and 2-(2-chloro-4-iodo-phenylamino)--cycloproplmethoxy-3,4-difluoro-benzenesulfonamide.

123. The method of claim 27, wherein said MEK inhibitor has a structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

124. The method of claim 59, wherein said MEK inhibitor has a structure selected from: 2-(4-ethynyl-2-methyl-phenylamino)-4-fluoro-benzoic acid; and 2-(3',5'-dichloro-biphenyl-4-ylamino)-benzoic acid.

125. The method of claim 95, wherein said MEK inhibitor has a structure selected from: 2-(2-chloro-4-iodo-phenylamino)-*N*-cyclopropylmethoxy-3,4-difluoro-5-sulfamoyl-benzamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-hydroxy-5-sulfamoyl-benzamide; C-(2-chloro-4-iodo-phenylamino)-*N*-cyclopropylmethoxy-dimethylsulfamoyl-difluoro-benzamide; *N*-cyclopropylmethoxy-dimethylsulfamoyl-difluoro-C-(4-iodo-2-methyl-phenylamino)-benzamide; and C-(2-chloro-4-iodo-phenylamino)-difluoro-(methoxy-methyl-sulfamoyl)-*N*-(2-morpholin-4-yl-ethoxy)benzamide.

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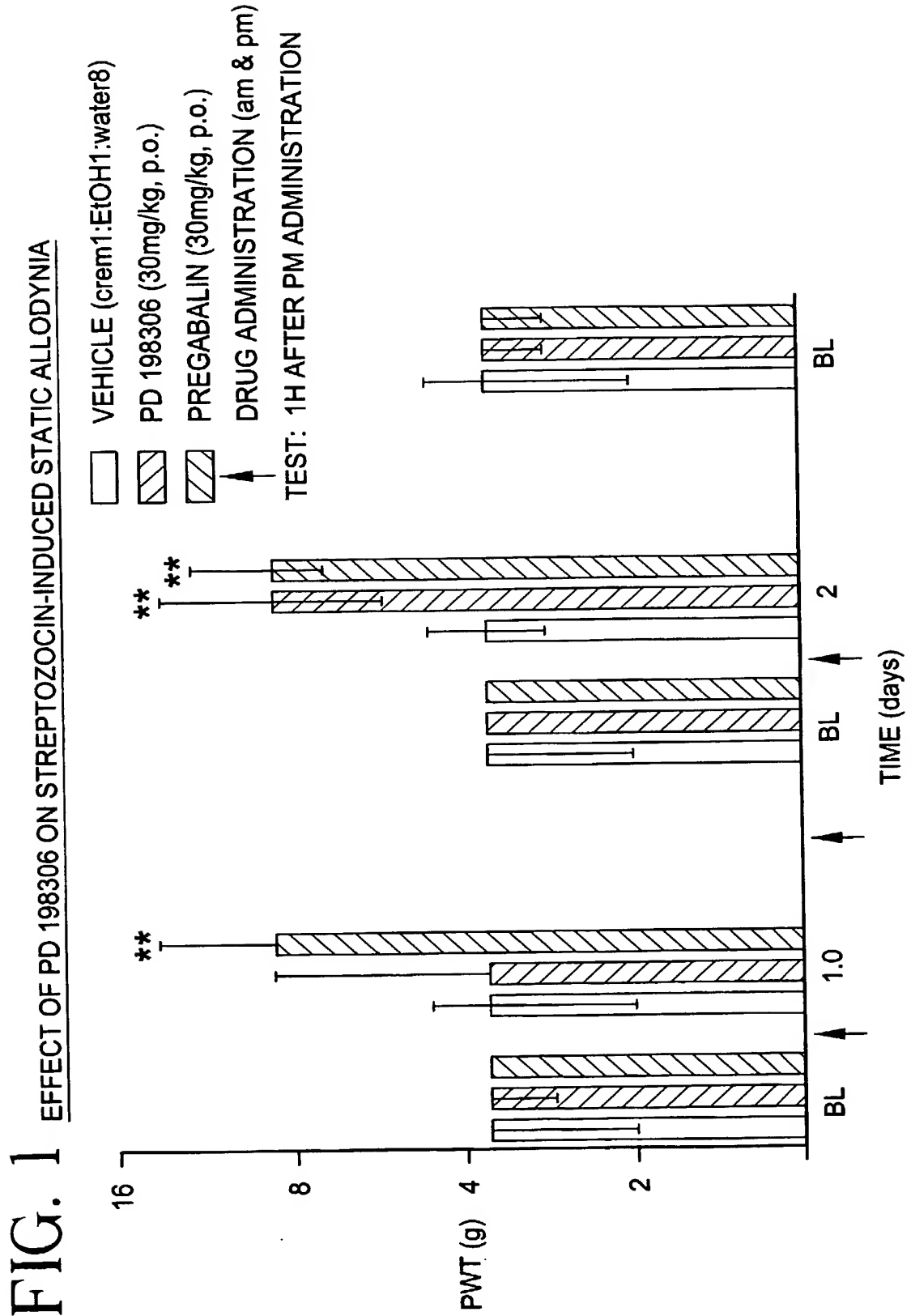
(54) Title: **METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS**

(57) Abstract: The invention features a method for treating chronic pain using a compound selected from formulae (I), (II)A, (I)B and (I)C.

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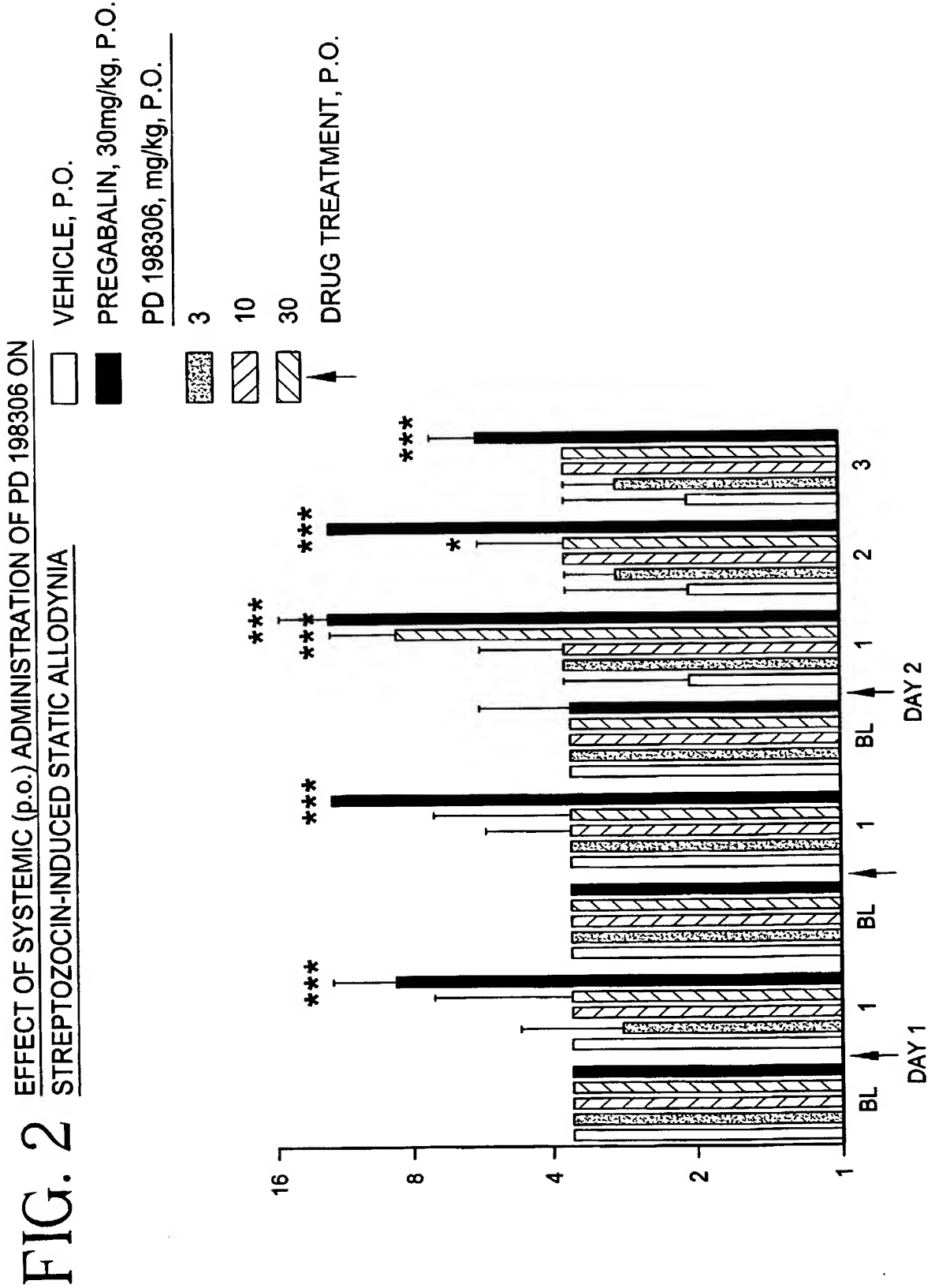
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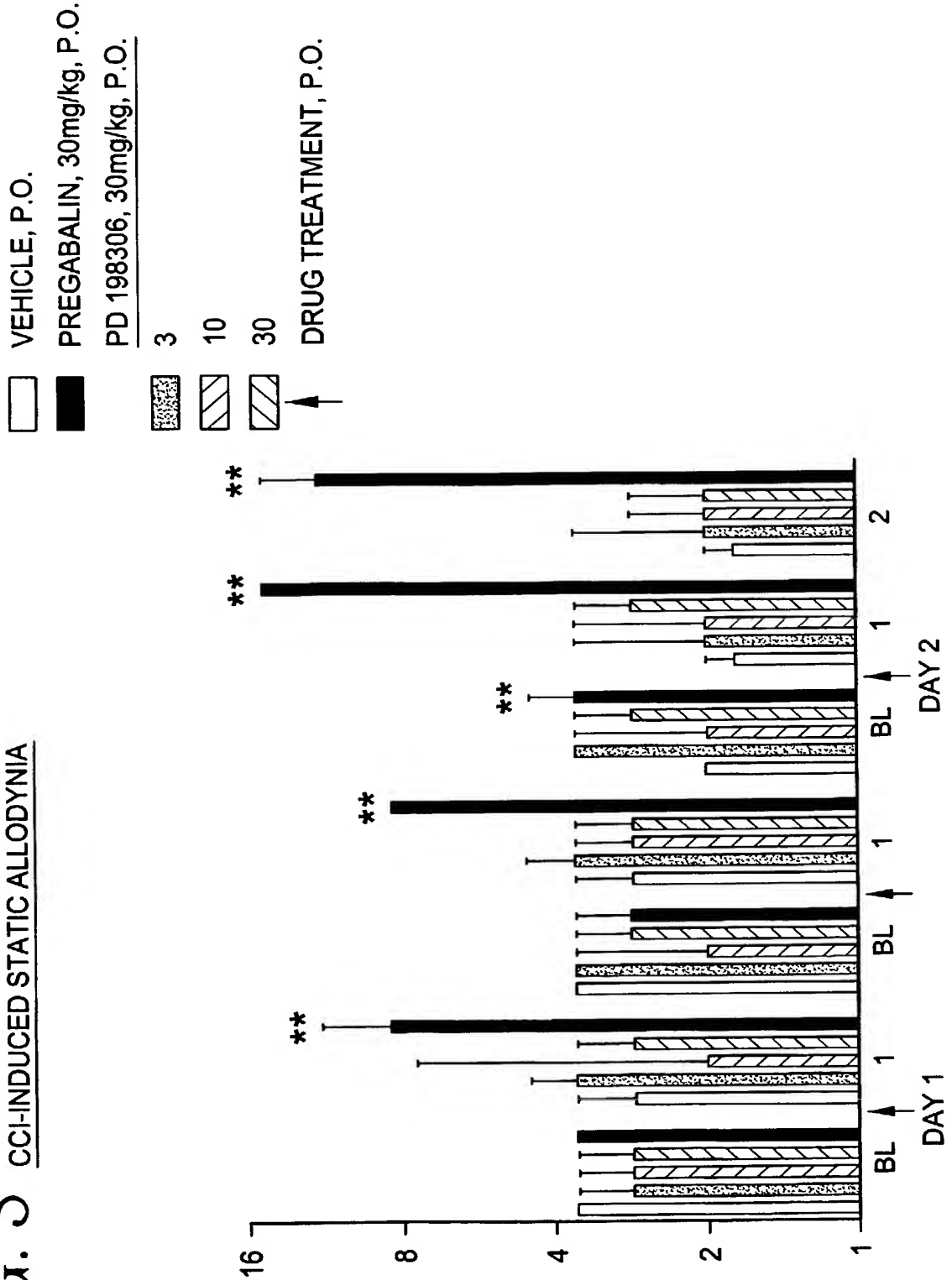
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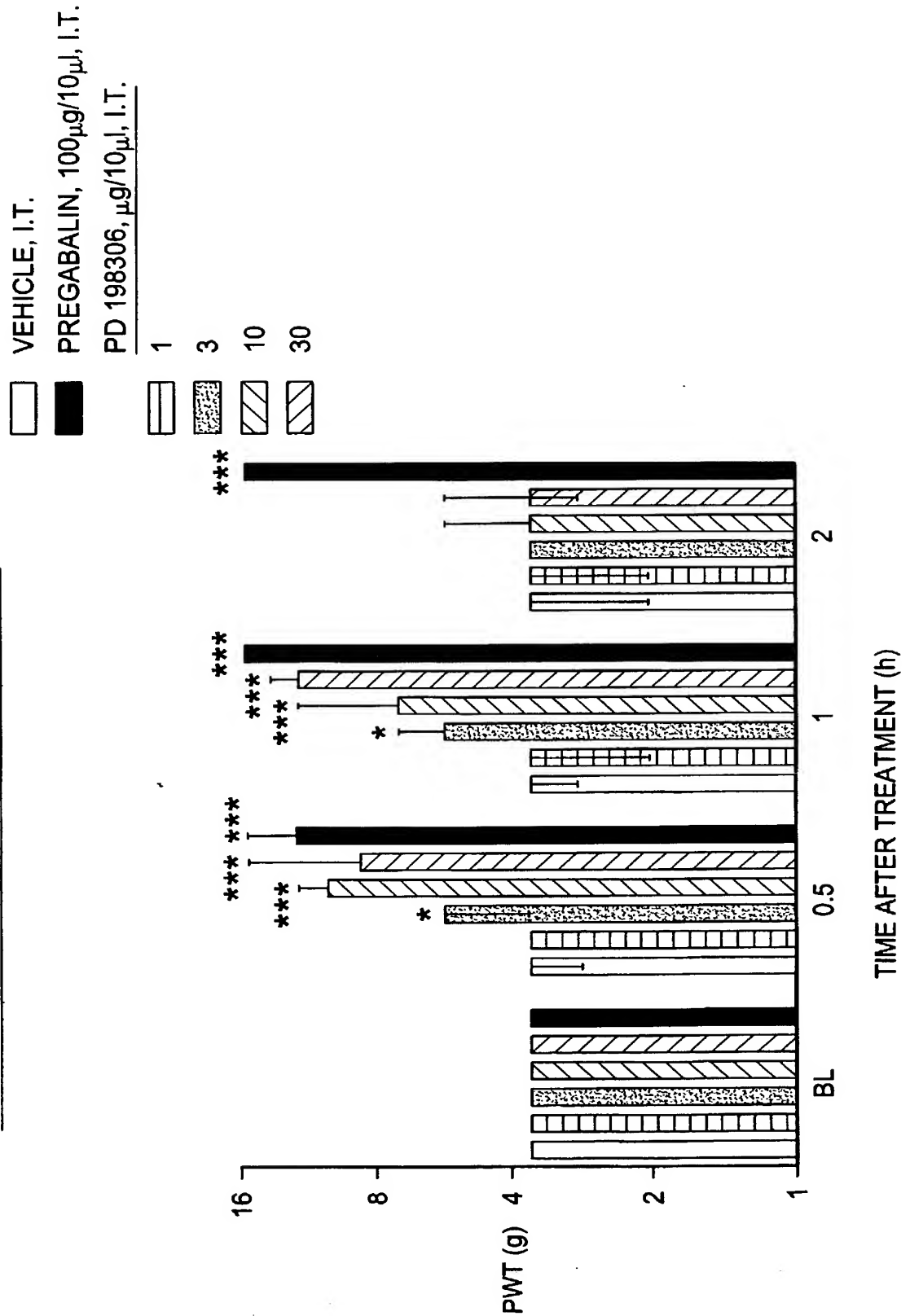


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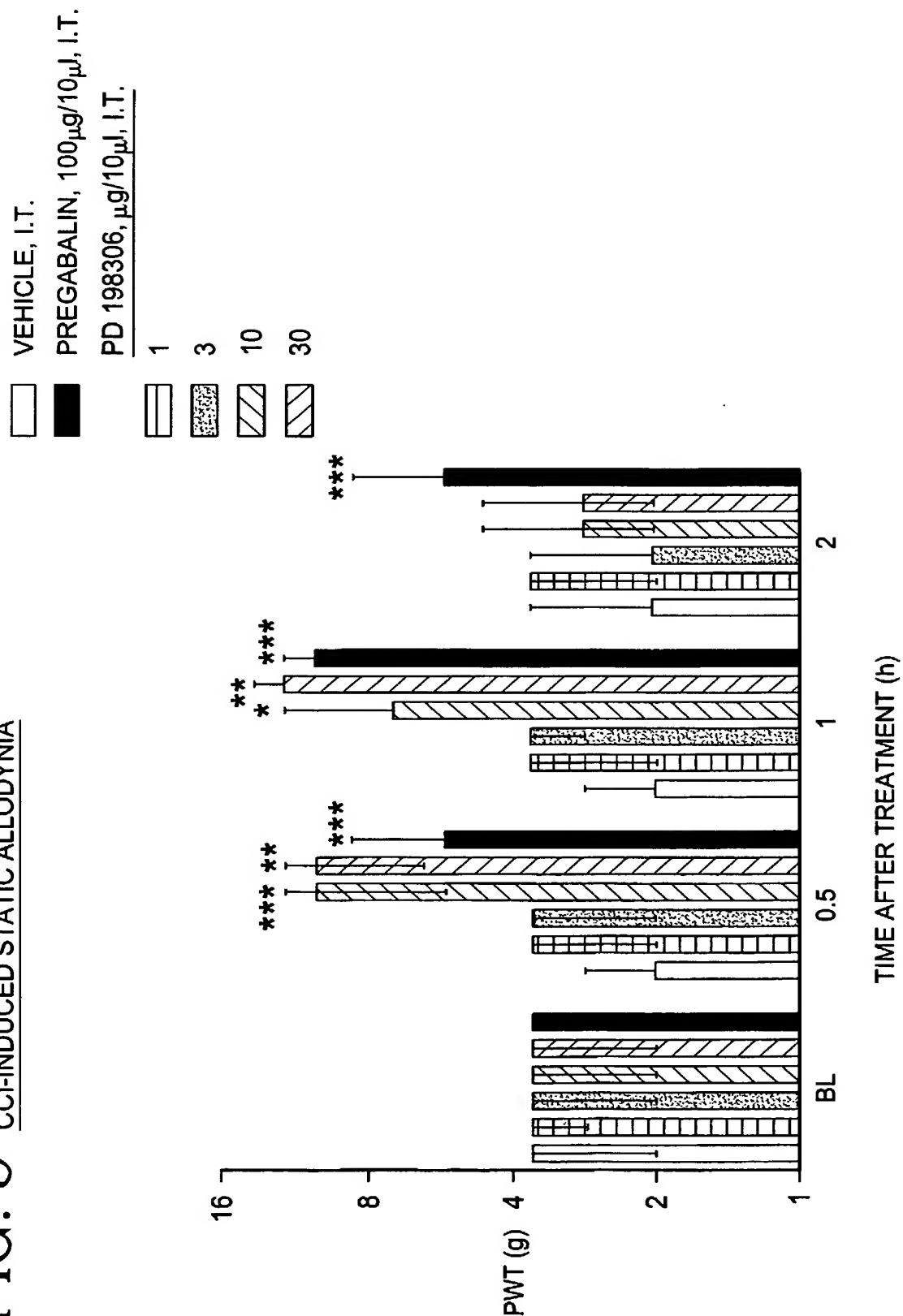
**FIG. 3** EFFECT OF SYSTEMIC (p.o.) ADMINISTRATION OF PD 198306 ON CCI-INDUCED STATIC ALLODYNIA



**FIG. 4** EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA



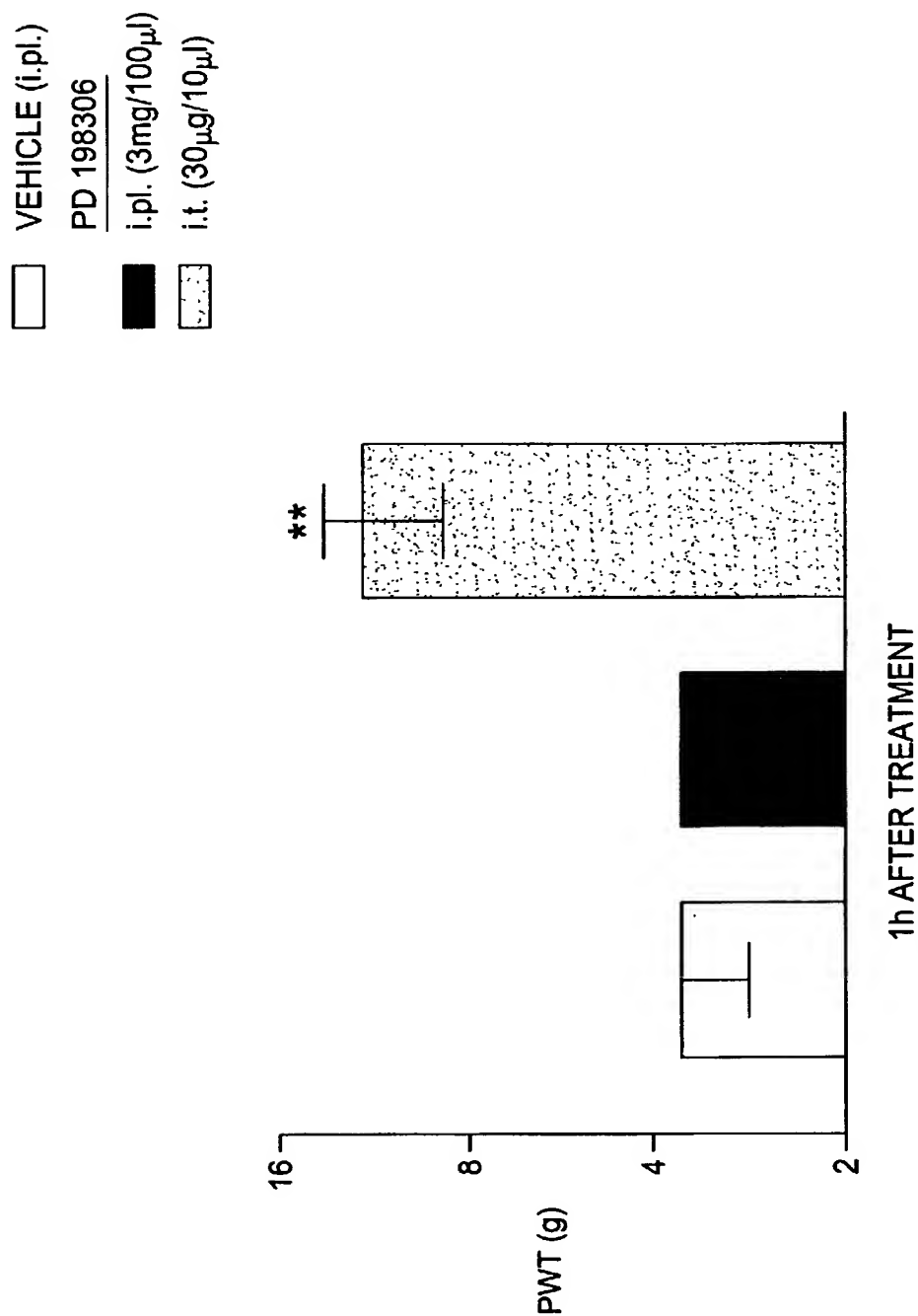
**FIG. 5** EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 198306 ON CCI-INDUCED STATIC ALLODYNIA



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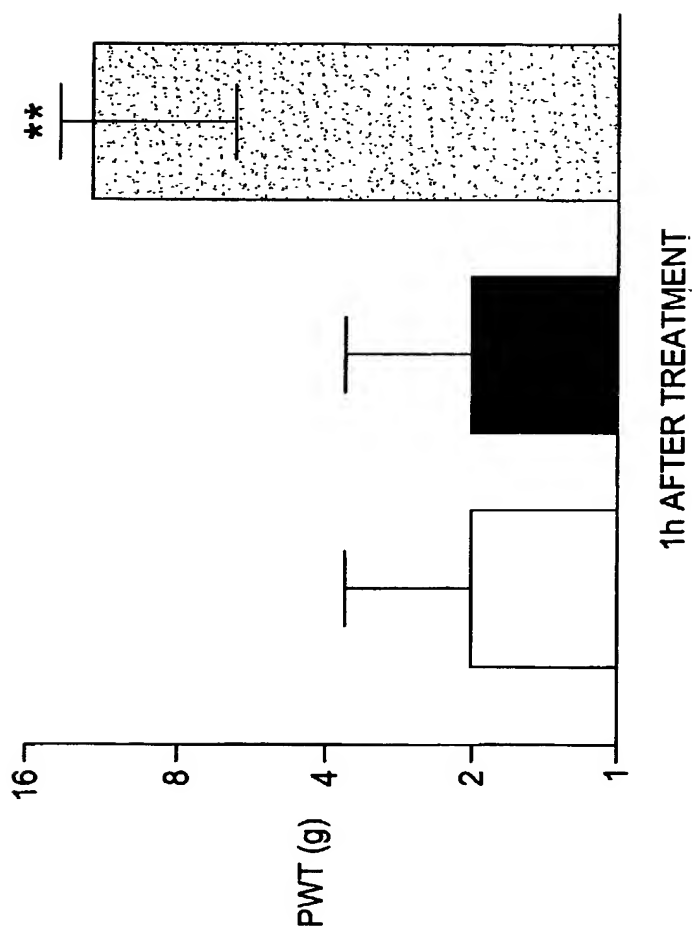
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**FIG. 6** EFFECT OF INTRAPLANTAR (i.pl.) ADMINISTRATION OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA

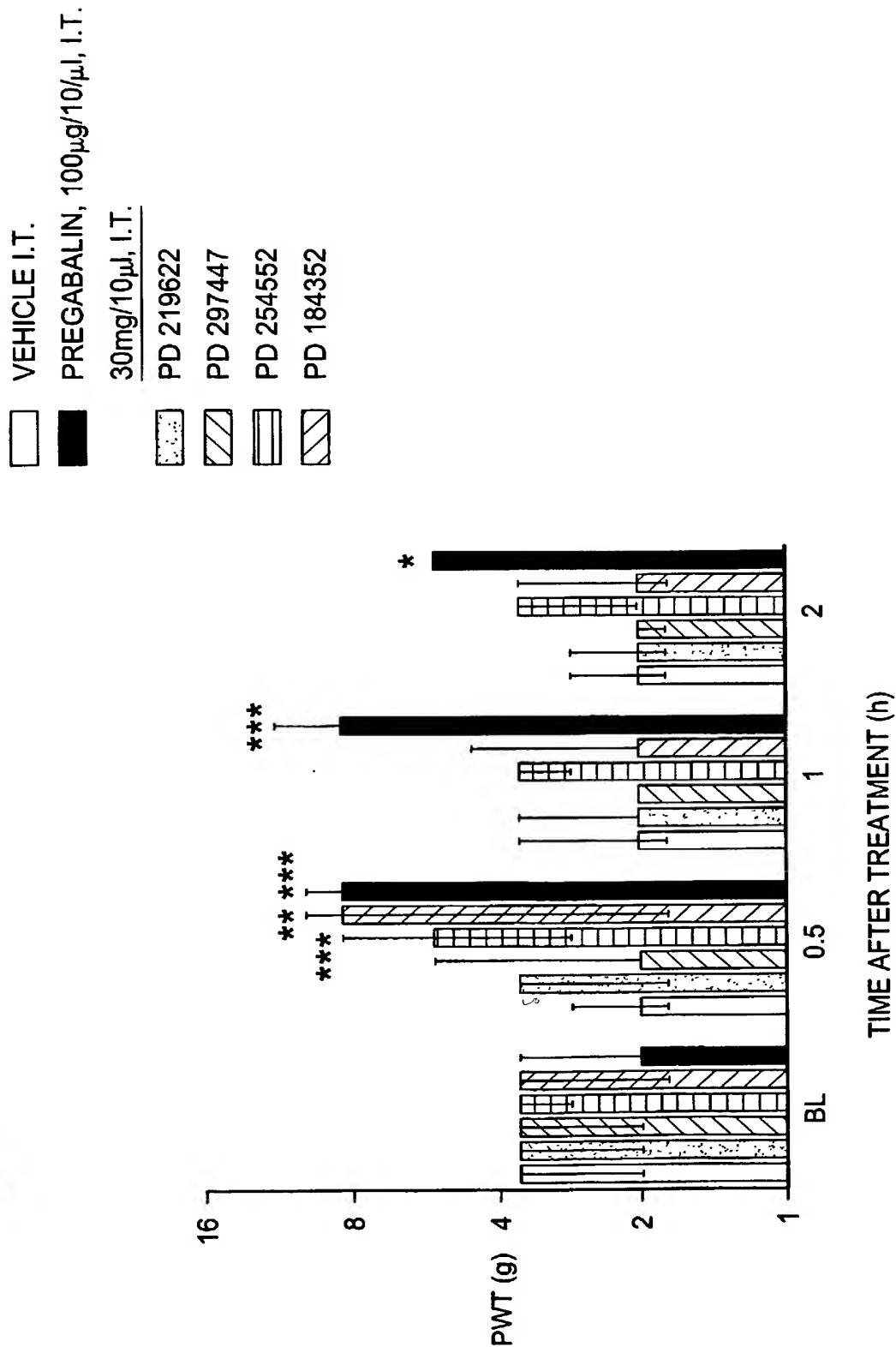


**FIG. 7** EFFECT OF INTRAPLANTAR (i.p.l.) ADMINISTRATION OF PD 198306 ON CCI-INDUCED STATIC ALLODYNIA

□ VEHICLE (i.p.l.)  
 PD 198306  
 ■ i.p.l. (3mg/100 $\mu$ l)  
 ▨ i.t. (30ug/10 $\mu$ l)



**FIG. 8** EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 219622, PD 297447, PD 184352, PD 254552 OR PREGABALIN ON CCI-INDUCED STATIC ALLODYNIA



## Declaration and Power of Attorney For Patent Application

### English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 05 July 2000 As United States Application No. \_\_\_\_\_ or PCT International  
Application Number PCT/US00/18348  
and was amended on \_\_\_\_\_

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a-d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications

Priority Not Claimed

(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/144,419</u> (Application Serial No.)	<u>16 July 1999</u> (Filing Date)	<u>60/144,658</u> (Application Serial No.)	<u>16 July 1999</u> (Filing Date)
<u>60/144,280</u> (Application Serial No.)	<u>16 July 1999</u> (Filing Date)	<u>60/144,659</u> (Application Serial No.)	<u>16 July 1999</u> (Filing Date)
<u>60/144,320</u> (Application Serial No.)	<u>16 July 1999</u> (Filing Date)	<u>60/144,655</u> (Application Serial No.)	<u>16 July 1999</u> (Filing Date)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

<u>PCT/US00/18348</u> (Application Serial No.)	<u>05 July 2000</u> (Filing Date)	<u>Pending</u> (Status) (patented, pending, abandoned)
<u>(Application Serial No.)</u>	<u>(Filing Date)</u>	<u>(Status)</u> (patented, pending, abandoned)
<u>(Application Serial No.)</u>	<u>(Filing Date)</u>	<u>(Status)</u> (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



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